রথের সমুদয় অঙ্গ-প্রত্যঙ্গই আমার সুবিদিত। সুতরাং স্থানোচিত জ্ঞানেই ইহা আমার প্রতিভাত হইবে।"

"রাজকুমার, তদ্রূপই যে-সকল ক্ষত্রিয় পণ্ডিত,... স্থানোচিত (প্রত্যুৎপন্ন) জ্ঞানেই আমার প্রতিভাত হয়। তাহার কারণ কী? রাজকুমার, তথাগতের সেই ধর্মধাতু (সর্বজ্ঞতা) সুপ্রতিবিদ্ধ (সুপরিজ্ঞাত) হইয়াছে, যেই ধর্মধাতুর সুপ্রতিবিদ্ধতা-হেতু স্থানোচিতভাবেই তথাগতের যাবতীয় প্রশ্নের সমাধান প্রতিভাত হয়।"

এইরূপ উক্ত হইলে অভয় রাজকুমার ভগবানকে বলিলেন, "আশ্চর্য ভন্তে,... আজ হইতে যাবজ্জীবন আমাকে শরণাগত উপাসকরূপে ধারণা করুন।"

অভয় রাজকুমার সূত্র সমাপ্ত

৯. বহু বেদনীয় সূত্র

৮৮. আমি এইরূপ শুনিয়াছি।

এক সময় ভগবান শ্রাবস্তীতে অনাথপিণ্ডিকের আরাম জেতবনে বাস করিতেছিলেন। তখন পঞ্চকংগ স্থপতি (সূত্রধর) যেখানে আয়ুষ্মান উদায়ী থাকেন, তথায় উপনীত হইলেন। তথায় উপস্থিত হইয়া আয়ুষ্মান উদায়ীকে অভিবাদন করিয়া একপ্রান্তে বসিলেন। একপ্রান্তে উপবিষ্ট পঞ্চকংগ স্থপতি আয়ুষ্মান উদায়ীকে বলিলেন, "ভন্তে, উদায়ি, ভগবান বেদনা কয় প্রকার বলিয়াছেন?"

"স্থপতি, (১) সুখ-বেদনা, (২) দুঃখ-বেদনা, (৩) অদুঃখ-অসুখ বেদনা; ভগবান এই তিন প্রকার বেদনা বলিয়াছেন।... ।"

"ভন্তে, উদায়ি, ভগবান তিন প্রকার বেদনা বলেন নাই, দুই প্রকার[১] বেদনা বলিয়াছেন—সুখ-বেদনা ও দুঃখ-বেদনা। ভন্তে, এই যে অদুঃখ-অসুখ বেদনা আছে, উহাকে ভগবান শান্ত, উত্তম সুখের অন্তর্গত বলিয়াছেন।"

দ্বিতীয়বারও আয়ুষ্মান উদায়ী পঞ্চকংগ স্থপতিকে বলিলেন, "স্থপতি,

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[১]। সুখ দুই প্রকার—বেদয়িত বা অনুভব সুখ, অবেদয়িত বা উপশান্ত সুখ। ইন্দ্রিয় ও বিষয় সুখ হইতে ক্রমে অষ্ট ধ্যান সমাপত্তি পর্যন্ত বেদয়িত সুখ। নিরোধসমাপত্তি—সংজ্ঞা-বেদনার নিরোধ হেতু উপশম সুখ। সুখ-দুঃখের অবসান ও দুঃখবিহীন হেতু সুখ নামে অভিহিত হয়। এই সূত্রে উভয়বিধ সুখ লক্ষ করিয়াই সুখময় বলা হইয়াছে। (প-সূ.)

ভগবান দুই প্রকার বেদনা বলেন নাই। ভগবান তিন প্রকার বেদনা বলিয়াছেন...।"

দ্বিতীয়বারও পঞ্চকংগ স্থপতি আয়ুষ্মান উদায়ীকে বলিলেন, "নহে, ভন্তে, উদায়ি,... শান্ত, উত্তম সুখের অন্তর্গত বলিয়াছেন।"

তৃতীয়বারও আয়ুষ্মান উদায়ী...।"

তৃতীয়বারও পঞ্চকংগ স্থপতি...।

আয়ুষ্মান উদায়ী পঞ্চকংগ স্থপতিকে বুঝাইতে পারিলেন না, পঞ্চকংগ স্থপতিও আয়ুষ্মান উদায়ীকে বুঝাইতে পারিলেন না।

৮৯. পঞ্চকংগ স্থপতির সহিত আয়ুষ্মান উদায়ীর এই আলোচনা আয়ুষ্মান আনন্দ শুনিতে পাইলেন। তখন আয়ুষ্মান আনন্দ যেখানে ভগবান তথায় গেলেন এবং ভগবানকে অভিবাদন করিয়া একপ্রান্তে বসিলেন। একপ্রান্তে উপবিষ্ট আয়ুষ্মান আনন্দ পঞ্চকংগের সহিত আয়ুষ্মান উদায়ীর যাহা কিছু আলোচনা হইয়াছে সেই সমস্ত ভগবানকে নিবেদন করিলেন। ইহা বলা হইলে ভগবান আয়ুষ্মান আনন্দকে বলিলেন, "আনন্দ পর্যায় (কারণ) থাকা সত্ত্বেও পঞ্চকংগ স্থপতি উদায়ীর ভাষণ অনুমোদন করিল না, আর পর্যায় (কারণ) থাকা সত্ত্বেও পঞ্চকংগ স্থপতি উদায়ীর ভাষণ অনুমোদন করিল না। আনন্দ, আমি পর্যায়বশত (কারণ ভেদে) বেদনা দুই প্রকার বলিয়াছি, তিন প্রকার, পাঁচ প্রকার, ছয় প্রকার, অষ্টাদশ প্রকার, ছয়ত্রিশ প্রকার, একশ আট প্রকারও বলিয়াছি। আনন্দ, এইরূপে পর্যায়ক্রমে আমি ধর্মোপদেশ করিয়াছি। আনন্দ, আমার পর্যায়ক্রমে উপদিষ্ট ধর্মে যাহারা পরস্পরের সুভাষিত, সুকথিত বাণীকে (ধর্মকে) স্বীকার করিবে না, মানিবে না, অনুমোদন করিবে না, তাহাদের পক্ষে ইহাই প্রত্যাশিত যে (সম্ভব যে) তাহারা ভণ্ডনজাত, কলহজাত, বিবাদাপন্ন হইয়া একে অন্যকে মুখশক্তি দ্বারা বিদ্ধ করিতে করিতে বাস করিবে। আনন্দ, এইরূপে আমাকর্তৃক ধর্ম পর্যায়ক্রমে দেশিত। আনন্দ, আমার... যাহারা পরস্পরের সুভাষিত, সুকথিত বাক্যকে উত্তমরূপে স্বীকার করিবে, মনন করিবে ও অনুমোদন করিবে তাহাদের... সম্মোদন করিতে করিতে বিবাদ রহিত হইয়া ক্ষীরোদকভূত অবস্থায় একে অন্যকে প্রিয়নেত্রে দেখিয়া বাস করিবে।"

৯০. "আনন্দ, এই পঞ্চ কামগুণ (ভোগ)। কী কী পঞ্চ? ইষ্ট, কান্ত, মনোহর, প্রিয়স্বরূপ কামসংযুক্ত মনোরঞ্জন চক্ষু-বিজ্ঞেয় রূপ;... শ্রোত-বিজ্ঞেয় শব্দ;... ঘ্রাণ-বিজ্ঞেয় গন্ধ;... জিহ্বা-বিজ্ঞেয় রস;... কায়-বিজ্ঞেয় স্পৃষ্টব্য। আনন্দ, এই পঞ্চ কামগুণ। আনন্দ, এই পঞ্চ কামগুণের সংস্রবে যে

সুখ-সৌমনস্য উৎপন্ন হয়, তাহাকেই কামসুখ বলা হয়।"

"আনন্দ, যদি কেহ এইরূপ বলে : প্রাণীগণ এই পর্যন্তই চরম সুখ-সৌমনস্য ভোগ করে, তাহার এই মত (সিদ্ধান্ত) আমি সমর্থন করি না। ইহার কারণ কী? আনন্দ, এই সুখ হইতে আরও সুন্দর ও উন্নততর (বিপুলতর) অপর সুখ আছে। আনন্দ, অন্য কোনো সুখ এই সুখ হইতে উজ্জ্বলতর ও উন্নততর? এখানে আনন্দ, ভিক্ষু... প্রথম ধ্যান লাভ করিয়া বাস করে। ইহাই আনন্দ, সে সুখ হইতে উজ্জ্বলতর ও উন্নততর অপর সুখ।"

"আনন্দ, যদি কেহ বলে... আমি সমর্থন করি না।... দ্বিতীয় ধ্যান লাভ করিয়া বাস করে।...।"

"আনন্দ, যদি কেহ বলে... তাহার এই মতও আমি সমর্থন করি না।... তৃতীয় ধ্যান লাভ করিয়া বাস করে।...।"

"আনন্দ, যদি কেহ ইহা বলে... আমি সমর্থন করি না।... চতুর্থ ধ্যান লাভ করিয়া বাস করে।...।"

"এইরূপে আনন্দ,... আকাশ-অনন্ত-আয়তন লাভ করিয়া বাস করে।...।... বিজ্ঞান-অনন্ত-আয়তন লাভ করিয়া বাস করে।...।... আকিঞ্চনায়তন লাভ করিয়া বাস করে।...।... নৈবসংজ্ঞা-না-অসংজ্ঞায়তন লাভ করিয়া বাস করে।...। আনন্দ, এখানে নৈবসংজ্ঞা-না-অসংজ্ঞায়তন সর্বতোভাবে অতিক্রমপূর্বক সংজ্ঞাবেদয়িত নিরোধকে অধিগত হইয়া বাস করে। ইহাই আনন্দ, সে সুখ হইতে উজ্জ্বলতম ও উন্নততম—অপর সুখ।"

৯১. "আনন্দ, সম্ভবত অন্যতীর্থিয় পরিব্রাজকগণ বলিতে পারেন, 'শ্রমণ গৌতম সংজ্ঞা বেদয়িত নিরোধ সম্বন্ধে বলেন, তাহাও সুখময় বলিয়া থাকেন। উহা কী? উহা কী প্রকার?' এইরূপবাদী অন্যতীর্থিয়গণকে ইহা বলা উচিত : 'বন্ধুগণ, ভগবান সুখ-বেদনা সম্পর্কেই উহাকে সুখময় বলেন নাই। কিন্তু বন্ধুগণ, যেখানে যেখানে (বেদয়িত বা অবেদয়িত) সুখ উপলব্ধ হয়, তথায় তাহাকেই তথাগত সুখান্তর্গত বলিয়া থাকেন'[১]।"

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[১]। সুখ দুই প্রকার—বেদয়িত (অনুভূতি) সুখ ও অবেদয়িত বা উপশম সুখ। পঞ্চকামগুণ সংস্তপর্শে ও অষ্ট লৌকিক সমাপত্তি বশে উৎপন্ন সুখের নাম বেদয়িত সুখ। চতুর্থধ্যান হইতে চারি অরূপধ্যান উপেক্ষা-বেদনাযুক্ত, তথাপি শান্তস্বভাব হেতু উহা সুখ পর্যায়ভুক্ত। নিরোধ সমাপত্তি অবেদয়িত সুখ। উহা সংজ্ঞা, বেদনা (বেদয়িত) প্রভৃতি মানস বা চেতন জগতের নিরোধ বা উপশম অবস্থা। [এ অবস্থায় সুখ নামের সার্থকতা কী?—'সব্বস্স দুক্খস্স সুখং পহাণং,' যাবতীয় দুঃখের প্রহাণই প্রকৃত সুখ।] সুতরাং যেকোনো সুখ হোক না কেন, দুঃখহীন ও সুখ-স্বরূপার্থে সুখ নামে অভিহিত হয়। (প-সূ.)

ভিক্ষুসংঘের শরণ গ্রহণ করছি। মাননীয় গৌতম, আজ হতে আজীবন আমাকে শরণাগত উপাসকরূপে ধারণা করুন।”

১১. বেদনা উৎপন্ন হয় পিত্ত, শ্লেষ্মা, বায়ু, সন্নিপাত আর ঋতুর পরিণামে; বিষম ব্যবহার, বাহ্যিক আক্রমণ ও কর্মবিপাক এই অষ্টবিধ কারণে।

প্রথম সূত্র সমাপ্ত।

২. একশ আট সূত্র

২৭০.১. “হে ভিক্ষুগণ, আমি তোমাদেরকে একশ আট ধর্ম পর্যায় সম্পর্কে দেশনা করব। তা শ্রবণ কর। হে ভিক্ষুগণ, একশ আট ধর্ম পর্যায় কী? হে ভিক্ষুগণ, পর্যায়ভেদে আমাকর্তৃক বেদনা দুই প্রকার উক্ত হয়েছে; পর্যায়ভেদে আমাকর্তৃক বেদনা তিন প্রকার, পাঁচ প্রকার, ছয় প্রকার, অষ্টাদশ প্রকার, ছয়ত্রিশ প্রকার, একশ আট প্রকারও উক্ত হয়েছে।”

২. “হে ভিক্ষুগণ, দুই প্রকার বেদনা কী কী? কায়িক (দৈহিক) ও চৈতসিক; এগুলোকে বলা হয় দুই প্রকার বেদনা। হে ভিক্ষুগণ, তিন প্রকার বেদনা কী কী? সুখ-বেদনা, দুঃখ-বেদনা ও অদুঃখ-অসুখ-বেদনা—হে ভিক্ষুগণ, এগুলোকে বলা হয় তিন প্রকার বেদনা। হে ভিক্ষুগণ, পাঁচ প্রকার বেদনা কী কী? সুখ-ইন্দ্রিয়, দুঃখ-ইন্দ্রিয়, সৌমনস্য-ইন্দ্রিয়, দৌর্মনস্য-ইন্দ্রিয়, উপেক্ষা-ইন্দ্রিয়—হে ভিক্ষুগণ, এগুলোকে বলা হয় পাঁচ প্রকার বেদনা। হে ভিক্ষুগণ, ছয় প্রকার বেদনা কী কী? চক্ষু-সংস্পর্শজ বেদনা, শ্রোত্র-সংস্পর্শজ বেদনা, ঘ্রাণ-সংস্পর্শজ বেদনা, জিহ্বা-সংস্পর্শজ বেদনা, কায়-সংস্পর্শজ বেদনা ও মনো-সংস্পর্শজ বেদনা। হে ভিক্ষুগণ, এগুলোকে বলা হয় ছয় প্রকার বেদনা। ভিক্ষুগণ, অষ্টাদশ প্রকার বেদনা কী কী? ছয় সৌমনস্য-উপবিচার, ছয় দৌর্মনস্য-উপবিচার ও ছয় উপেক্ষা-উপবিচার। ভিক্ষুগণ, এগুলোকে বলা হয় অষ্টাদশ প্রকার বেদনা। ভিক্ষুগণ, ছয়ত্রিশ প্রকার বেদনা কী কী? ছয় প্রকার সাংসারিক জীবনের সৌমনস্য (মানসিক সুখ)[১], ছয় প্রকার নিষ্কাম জীবনের সৌমনস্য[২]; ছয় প্রকার সাংসারিক জীবনের দৌর্মনস্য (মানসিক দুঃখ), ছয় প্রকার নিষ্কাম জীবনের দৌর্মনস্য; ছয় প্রকার সাংসারিক জীবনের উপেক্ষা, ছয় প্রকার নিষ্কাম জীবনের উপেক্ষা। হে ভিক্ষুগণ, এগুলোকে বলা হয় ছয়ত্রিশ প্রকার বেদনা। ভিক্ষুগণ,

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[১]। ছয় গৃহীজনোচিত সৌমনস্য।

[২]। ছয় নৈষ্ক্রম্য নিশ্রিত সৌমনস্য।

একশ আট প্রকার বেদনা কী কী? অতীতকালের ছত্রিশ প্রকার বেদনা, ভবিষ্যৎকালের ছত্রিশ প্রকার বেদনা আর বর্তমানকালের ছত্রিশ প্রকার বেদনা। ভিক্ষুগণ, এগুলোকে বলা হয় একশ আট প্রকার বেদনা। হে ভিক্ষুগণ, ইহাই একশ আট প্রকার ধর্ম পর্যায়।"

দ্বিতীয় সূত্র সমাপ্ত।

৩. অন্যতর ভিক্ষু সূত্র

২৭১. ১. অতঃপর জনৈক ভিক্ষু যেখানে ভগবান সেখানে উপস্থিত হয়ে ভগবানকে অভিবাদন করে একপাশে উপবেশন করলেন। একপাশে উপবিষ্ট সেই ভিক্ষু ভগবানকে বললেন, "ভন্তে, বেদনা কী? বেদনা-সমুদয় (উৎপত্তি) কী? বেদনা সমুদয়গামী প্রতিপদা (উপায়) কী? বেদনা-নিরোধ কী? বেদনা-নিরোধগামী প্রতিপদা কী? বেদনার আস্বাদ কী, আদীনব (দোষ) কী, নিঃসরণ (মুক্তি) কী?"

২. "হে ভিক্ষু, বেদনা এই তিন প্রকার। সুখ-বেদনা, দুঃখ-বেদনা, অদুঃখাসুখ-বেদনা। হে ভিক্ষু, এগুলোকে বলা হয় বেদনা। স্পর্শ সমুদয় হতে বেদনা সমুদয় (উদয়) হয়। তৃষ্ণা বেদনা সমুদয়গামিনী প্রতিপদা। স্পর্শের নিরোধে বেদনা নিরোধ হয়। এই আর্য অষ্টাঙ্গিক মার্গই বেদনা নিরোধগামিনী প্রতিপদা (বেদনা নিরোধের উপায়) যথা—সম্যক দৃষ্টি, সম্যক সংকল্প, সম্যক বাক্য, সম্যক কর্ম, সম্যক আজীব (জীবিকা), সম্যক প্রচেষ্টা, সম্যক স্মৃতি, সম্যক সমাধি। বেদনা হেতু যে সুখ-সৌমনস্য উৎপন্ন হয়, তা-ই বেদনার আস্বাদ; বেদনা যে অনিত্য, দুঃখপূর্ণ ও পরিবর্তনশীল; ইহাকে বলা হয় বেদনার আদীনব (দোষ)। বেদনা সম্পর্কে যা ছন্দ রাগ দমন, ছন্দরাগ পরিহার; তাই বেদনা হতে নিঃসরণ (মুক্তি)।"

তৃতীয় সূত্র সমাপ্ত।

৪. পূর্ব সূত্র

২৭২. ১. "হে ভিক্ষুগণ, সম্বোধি লাভের পূর্বে অনভিসম্বুদ্ধ ও বোধিসত্ত্ব অবস্থায় আমার মনে এই চিন্তা উদিত হয়েছিল—বেদনা কী? বেদনা-সমুদয় কী? বেদনা-সমুদয়গামিনী প্রতিপদা কী? বেদনা-নিরোধ কী? বেদনা নিরোধগামী প্রতিপদা কী? বেদনার আস্বাদ কী, আদীনব (দোষ) কী, নিঃসরণ কী?"

২. "হে ভিক্ষুগণ, তখন আমার যথাযথ মনস্কারে প্রজ্ঞার উদয় হলো—

৩. শূন্যতা-বর্গ

১. ক্ষুদ্র শূন্যতা সূত্র

আমি এইরূপ শুনিয়াছি।

এক সময় ভগবান শ্রাবস্তী-সমীপে পূর্বারামে মৃগার মাতার প্রাসাদে অবস্থান করিতেছিলেন। আয়ুষ্মান আনন্দ সায়াহ্ন সময়ে সমাধি হইতে উঠিয়া ভগবানের নিকট উপস্থিত হইলেন, উপস্থিত হইয়া ভগবানকে অভিবাদন করিয়া একান্তে উপবেশন করিলেন। একান্তে উপবিষ্ট হইয়া আয়ুষ্মান আনন্দ ভগবানকে বলিলেন, ভদন্ত, এক সময় ভগবান শাক্যদের মধ্যে অবস্থান করিতেছিলেন। নগরক একটি শাক্যদের নিগম। তথায় ভগবানের নিকট হইতে আমার দ্বারা এরূপ শ্রুত ও প্রতিগৃহীত হইয়াছে : "আনন্দ, আমি শূন্যতা বিষয়ে ভাবনা করিয়া এখন তাহাতে পর্যাপ্তরূপে অবস্থান করিতেছি।" ভদন্ত, আমার দ্বারা কি তাহা সুশ্রুত, সুগৃহীত, সুমনোনিবিষ্ট ও সুচিন্তিত হইয়াছে?

নিশ্চিয়ই, আনন্দ, তোমার দ্বারা ইহা সুশ্রুত... সুচিন্তিত হইয়াছে। পূর্বে ও বর্তমানে শূন্যতা বিহারের দ্বারা পর্যাপ্তরূপে অবস্থান করিতেছি। যেমন, এই মৃগারমাতার প্রাসাদ হস্তি, গো, অশ্ব, ঘোটকী, স্বর্ণরৌপ্য ও স্ত্রী পুরুষের সমাবেশশূন্য (বর্জিত), আবার ইহা ভিক্ষুসংঘ-হেতু একত্ব[১] বিষয়ে অশূন্যতা। ঠিক এইরূপে, আনন্দ, ভিক্ষু গ্রাম-সংজ্ঞায়[২], মনুষ্য-সংজ্ঞায় মনোনিবেশ না করিয়া অরণ্যসংজ্ঞা-হেতু একত্বে মনোনিবেশ করেন। অরণ্য-সংজ্ঞায় তাঁহার চিত্ত প্রস্কন্দিত (অবতীর্ণ) হয়, শান্ত হয়, স্থিতি লাভ করে এবং বিমুক্ত হয়। তিনি প্রকৃষ্টরূপে জানেন—গ্রাম্য-জীবন ও মনুষ্যজীবন-হেতু যে-সকল দুর্বিপাক হইতে পারে সেই সকল এখানে নাই। এই দুর্বিপাকমাত্র আছে যাহা অরণ্যজীবন-হেতু একত্ব। তিনি প্রকৃষ্টরূপে জানেন—গ্রাম-সংজ্ঞাজনিত এই সংজ্ঞা শূন্য, মনুষ্য-সংজ্ঞাজনিত এই সংজ্ঞা শূন্য। অরণ্য-সংজ্ঞাজনিত একত্বে ইহা শূন্যতা নহে। তথায় যাহা নাই, তাহাকে তিনি শূন্য বলিয়া সম্যকরূপে দর্শন করেন। আর তথায় যাহা অবশিষ্ট আছে, সেই সম্পর্কে তিনি প্রকৃষ্টরূপে জানেন, তাহা বলিয়া ইহা আছে। আনন্দ, এইরূপে তাঁহার নিকট ইহা যথার্থ, অবিপর্যস্ত, পরিশুদ্ধ

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[১]। একত্তংতি একভাবং—অর্থাৎ ভিক্ষুসংঘজনিত একাকিত্ব, প. সূ।

[২]। গ্রাম-সংক্রান্ত চিন্তায়।

শূন্যতা জ্ঞান বলিয়া প্রতীত হয়।

পুনরায়, আনন্দ, ভিক্ষু মনুষ্য-সংজ্ঞায় ও অরণ্য-সংজ্ঞায় মনোনিবেশ না করিয়া পৃথিবী-সংজ্ঞা-হেতু একত্বে মনোনিবেশ করেন। তাঁহার পৃথিবী সংজ্ঞায় চিত্ত অবতীর্ণ হয়, শান্ত হয়, স্থিতি লাভ করে ও বিমুক্ত হয়। আনন্দ, যেমন, শত লৌহশূল দ্বারা বিদ্ধ হইয়া বৃষচর্ম মসৃণতাহীন হয়। ঠিক এইরূপে এই পৃথিবীর শুষ্ক ও জলাভূমি, নদী ও দুর্গমস্থান, কণ্টকপূর্ণ গুল্ম, পর্বত ও অসমতল ভূমি ইত্যাদি কোনো কিছুতে মনোনিবেশ না করিয়া পৃথিবী-সংজ্ঞাহেতু একাত্বে মনোনিবেশ করেন। তাঁহার পৃথিবী-সংজ্ঞায় চিত্ত অবতীর্ণ... শূন্যতাজ্ঞান হয়।

পুনরায়, আনন্দ, ভিক্ষু অরণ্য-সংজ্ঞায় বা পৃথিবী-সংজ্ঞায় মনোনিবেশ না করিয়া আকাশ-অনন্ত আয়তন-সংজ্ঞাহেতু একত্বে মনোনিবেশ করেন। তাঁহার আকাশ-অনন্ত আয়তন সংজ্ঞায় চিত্ত অবতীর্ণ হয়... শূন্যতাজ্ঞান হয়। বিজ্ঞান-অনন্ত-আয়তন-সংজ্ঞা, আকিঞ্চন-আয়তন-সংজ্ঞা, নৈবসংজ্ঞা-না-অসংজ্ঞায়তন-সংজ্ঞা সম্পর্কেও এইরূপ।

পুনরায়, আনন্দ, ভিক্ষু আকিঞ্চন-আয়তন-সংজ্ঞা ও নৈবসংজ্ঞা-না-অসংজ্ঞায়তন সংজ্ঞায় মনোনিবেশ না করিয়া অনিমিত্ত চেতঃসমাধি-হেতু একত্বে মনোনিবেশ করেন। তাঁহার অনিমিত্ত চেতঃসমাধিতে চিত্ত অবতীর্ণ... এই দুর্বিপাক মাত্র আছে যাহা এই কায়হেতু ষড়ায়তনীয় জীবিত প্রত্যয়। তিনি প্রকৃষ্টরূপে জানেন... শূন্যতা জ্ঞান বলিয়া প্রতীত হয়।

পুনরায়, আনন্দ, ভিক্ষু... বিমুক্ত হয়। তিনি প্রকৃষ্টরূপে জানেন—এই অনিমিত্ত চেতঃসমাধি অভিসংস্কৃত (নির্মিত) এবং চিত্তের দ্বারা উদ্ভাবিত। যাহা কিছু অভিসংস্কৃত ও উদ্ভাবিত তাহা অনিত্য ও নিরোধ-ধর্মী ইহা বুঝিতে পারেন। তাঁহার এইভাবে জানিবার ও দেখিবার ফলে কামাসব, ভবাসব ও অবিদ্যাসব হইতে চিত্ত বিমুক্তি হয়। বিমুক্তিতে বিমুক্ত বলিয়া এই জ্ঞান হয়: পুনর্জন্ম বিনষ্ট হইয়াছে, ব্রহ্মচর্য পালিত হইয়াছে, সমস্ত করণীয় সম্পাদিত হইয়াছে, ইহার পরে আর এইখানে আসিতে হইবে না বলিয়া জানেন। তিনি প্রকৃষ্টরূপে ইহা জানেন—যেসমস্ত দুর্বিপাক কামাসব-হেতু হয় তাহা এখানে নাই।... শূন্যতা-জ্ঞান বলিয়া প্রতীত হয়। আনন্দ, অতীতের যে-সকল শ্রমণ-ব্রাহ্মণ পরিশুদ্ধ পরম ও অনুত্তর শূন্যতা লাভ করিয়া তাহাতে অবস্থান করিয়াছিলেন, যে-সকল অনাগত শ্রমণ-ব্রাহ্মণ... অবস্থান করিবেন, যে-সকল

বর্তমান শ্রমণ-ব্রাহ্মণ... অবস্থান করেন, তাঁহারা সকলেই সেই শূন্যতা[১] লাভ করিয়া তাহাতে অবস্থান করিয়াছিলেন, করিবেন ও করেন। সুতরাং আনন্দ, পরিশুদ্ধ ও পরম অনুত্তর শূন্যতা লাভ করিয়া তাহাতে অবস্থান করিব"— ইহাই তোমাদের শিক্ষণীয়।

ভগবান ইহা বলিলেন। আয়ুষ্মান আনন্দ ভগবানের ভাষণে আনন্দ প্রকাশ করিলেন।

ক্ষুদ্র শূন্যতা সূত্র সমাপ্ত

২. মহাশূন্যতা সূত্র

আমি এইরূপ শুনিয়াছি।

এক সময় ভগবান শাক্যরাজ্যে অবস্থান করিতেছিলেন কপিলবাস্তু সমীপে ন্যগ্রোধারামে। ভগবান পূর্বাহ্নে বহির্গমন বাস পরিধান করিয়া, পাত্রচীবর লইয়া ভিক্ষার জন্য কপিলবাস্তুতে প্রবেশ করিলেন। কপিলবাস্তুতে ভিক্ষাচর্যা করিয়া প্রত্যাবর্তনপূর্বক ভোজনান্তে কাড়ক্ষেমক শাক্যের বিহারে দিবা বিহারের জন্য উপস্থিত হইলেন। সেই সময়ে কাড়ক্ষেমক শাক্যের বিহারে বহু শয়নাসনের শয্যাদ্রব্য-সমন্বিত বাসস্থানের ব্যবস্থা ছিল। ভগবান সেইসকল শয়নাসন দেখিলেন। দেখিয়া ভগবান চিন্তা করিলেন, কাড়ক্ষেমক শাক্যের বিহারে বহু শয়নাসনের ব্যবস্থা আছে। "এখানে অনেক ভিক্ষু থাকে কি?" এই চিন্তা করিলেন।

সেই সময়ে আয়ুষ্মান আনন্দ বহু ভিক্ষুর সহিত ঘটায় শাক্যের বিহারে[২] চীবরকর্ম করিতেছিলেন। ভগবান সায়াহ্নে সময়ে সমাধি হইতে উঠিয়া ঘটায় শাক্যের বিহারে উপস্থিত হইয়া নির্দিষ্ট আসনে উপবেশন করিলেন। উপবেশন করিয়া ভগবান আয়ুষ্মান আনন্দকে আহ্বান করিলেন, আনন্দ, কাড়ক্ষেমক শাক্যের বিহারে বহু শয়নাসনের ব্যবস্থা আছে। এখানে বহু ভিক্ষু বাস করে কি?

ভদন্ত, কাড়ক্ষেমক শাক্যের বিহারে বহু শয়নাসনের ব্যবস্থা আছে। এখানে অনেক ভিক্ষু বাস করেন। এখন আমাদের চীবর প্রস্তুত করিবার সময়।

আনন্দ, কোনো ভিক্ষুর সঙ্গণিকারাম[৩], সঙ্গণিকারত, সঙ্গণিকানুলিপ্ত বা

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[১]। শূন্যতা ফলসমাপত্তি—প.সূ।

[২]। ইহা ন্যগ্রোধারামে নির্মিত অন্য একটি বিহার—প.সূ.

[৩]। সঙ্গণিকারাম অর্থে স্বীয় দলের সদস্যদের মধ্যে আনন্দলাভী।

গণারাম[১], গণরত, গণসম্মুদিত হওয়া শোভা পায় না। বাস্তবিক, আনন্দ, ইহা সম্ভব নহে যেকোনো ভিক্ষু সঙ্গণিকারাম... গণসম্মুদিত হইয়া অনায়াসে, স্বেচ্ছা ক্রমে ও আনন্দ-সহকারে নৈষ্ক্রম্যসুখ, বিবেকসুখ, উপশমসুখ ও সম্বোধিসুখ লাভ করিবেন। ইহা সম্ভব যে ভিক্ষুগণ হইতে ব্যপকৃষ্ট (পৃথক) হইয়া একাকী বিচরণ করেন, তাঁহার নিকট প্রত্যাশা করা যে তিনি অনায়াসে, স্বেচ্ছাক্রমে ও আনন্দ-সহকারে নৈষ্ক্রম্য-সুখ... সম্বোধি-সুখ লাভ করিবেন। বাস্তবিক আনন্দ, ইহা সম্ভব নহে যে কোনো ভিক্ষু সঙ্গণিকারাম... গণসম্মুদিত হইয়া অনায়াসে, স্বেচ্ছা-ক্রমেও আনন্দ-সহকারে সামায়িক[২] কান্ত (মনোজ্ঞ) চেতোবিমুক্তি বা অসামায়িক অবিচল চেতোবিমুক্তি লাভ করিয়া তাহাতে অবস্থান করেন। বরং ইহা সম্ভব যে ভিক্ষুগণ হইতে ব্যপকৃষ্ট হইয়া... অবস্থান করিবেন। আনন্দ, আমি কোনো একটি রূপ[৩] দেখি না যেখানে রাগ বশে আনন্দরত রূপের বিপরিণাম ও অন্যথাভাবহেতু শোক, রোদন, দুঃখ, দৌর্মনস্য, উপয়াস উৎপন্ন হইবে না।

কিন্তু, আনন্দ, এই অবস্থান যাহা সর্বনিমিত্তের অমনোনিবেশ-হেতু অধ্যাত্মশূন্যতা লাভ করিয়া অবস্থান, তাহা তথাগতের দ্বারা অভিসম্বুদ্ধ হইয়াছে। যদি এইরূপে অবস্থানরত তথাগতের নিকট ভিক্ষু-ভিক্ষুণী, উপাসক, উপাসিকা, রাজা, রাজমহামাত্য, তীর্থিক ও তীর্থিক শিষ্যগণ উপস্থিত হন। বিবেকাভিমুখী, বিবেকপ্রবণ, বিবেক-প্রাগ্‌ভার, ব্যপকৃষ্ট, নৈষ্ক্রম্যাভিরত চিত্তে আসবের ভিত্তি বিনষ্ট করিয়া তথাগত তাহাদিগকে উৎসাহব্যঞ্জক কথা বলেন। সুতরাং, আনন্দ, যদি কোনো ভিক্ষু আকাঙ্ক্ষা করেন, 'অধ্যাত্মশূন্যতা লাভ করিয়া তাহাতে অবস্থান করিব' তাহা হইলে সেই ভিক্ষুর দ্বারা চিত্তকে সংস্থাপিত, সন্নিবিষ্ট, একাগ্র ও সমাহিত করা উচিত।

আনন্দ, ভিক্ষু কিরূপে অধ্যাত্মভাবে চিত্তকে প্রতিষ্ঠিত, সন্নিবিষ্ট একাগ্র ও সুবিন্যস্ত করেন? এই স্থলে ভিক্ষু কাম হইতে বিবিক্ত হইয়া, অকুশলধর্ম হইতে বিবিক্ত হইয়া সবির্তক সবিচার বিবেজক প্রীতিসুখমণ্ডিত প্রথম ধ্যান লাভ করিয়া তাহাতে অবস্থান করেন। বির্তক-বিচার উপশমে অধ্যাত্মসম্প্রসাদী, চিত্তের একাগ্রভাব আনয়নকারী অবির্তক, অবিচার,

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[১]। বিভিন্ন দলে আনন্দলাভী।

[২]। অপ্পিতপ্পতি সময়ে কিলেসেহি বিমুক্তং—প.সূ।

[৩]। বুদ্ধঘোষের মতে শরীর, প.সূ।

সমাধিজ প্রীতিসুখমণ্ডিত দ্বিতীয় ধ্যান... তৃতীয় ধ্যান, চতুর্থ ধ্যান লাভ করিয়া তাহাতে অবস্থান করেন। এইরূপে আনন্দ, ভিক্ষু অধ্যাত্মভাব চিত্তকে প্রতিষ্ঠিত... সুবিন্যস্ত করেন।

তিনি অধ্যাত্ম শূন্যতাতে মনোনিবেশ করেন, অধ্যাত্ম শূন্যতায় মনোনিবেশ করিবার জন্য অধ্যাত্ম শূন্যতা হইতে চিত্ত প্রস্কন্দিত হয় না, প্রশান্তি ও স্থিতি লাভ করে না এবং বিমুক্তি লাভ করে না। ইহাতে ভিক্ষু প্রকৃষ্টরূপে জানেন, অধ্যাত্ম শূন্যতায় মনোনিবেশ করার জন্য আমার চিত্ত... বিমুক্ত হয় না। এইভাবে তিনি সম্প্রজ্ঞাত হন। তিনি বহির্শূন্যতায় মনোনিবেশ করেন, তিনি অধ্যাত্ম-বহির্শূন্যতায় মনোনিবেশ করেন, তিনি অনিঞ্জে (সমাধি) মনোনিবেশ করেন, অনিঞ্জে মনোনিবেশ করার জন্য তাঁহার চিত্ত... বিমুক্তি লাভ করে না। ইহাতে তিনি সম্প্রজ্ঞাত হন। আনন্দ, পূর্ব সমাধি নিমিত্তে ভিক্ষুর অধ্যাত্মভাব চিত্তকে সংস্থাপিত, সন্নিবিষ্ট, একাগ্র ও সমাহিত করা উচিত। তিনি অধ্যাত্ম শূন্যতায় মনোনিবেশ করেন... বিমুক্তি লাভ করে না। ইহাতে ভিক্ষু প্রকৃষ্টরূপে জানেন... অনিঞ্জ হইতে চিত্ত প্রস্কন্দিত হয়... এইরূপে তিনি সম্প্রজ্ঞাত হন।

যদি, আনন্দ, সেই ভিক্ষুর এইভাবে অবস্থান করিবার সময় চঙ্ক্রমণের জন্য চিত্ত নমিত হয়, তিনি চঙ্ক্রমণ করেন এবং এইরূপ চিন্তা করেন, 'এইরূপে চঙ্ক্রমণকালে কোনো অভিধ্যা, দৌর্মনস্য, পাপ ও অকুশলধর্ম আমার মধ্যে অনুস্রাবিত হইবে না' ইহাতে তিনি সম্প্রজ্ঞাত হন। সেই ভিক্ষুর এইভাবে বিহার করিবার সময়, দাঁড়াইবার জন্য... উপবেশনের জন্য... শয়নের জন্য... ইহাতে তিনি সম্প্রজ্ঞাত হন। যদি ভিক্ষুর এইরূপে অবস্থান করিবার সময় এই চিন্তা করিয়া ভাষণের জন্য চিত্ত নমিত করেন, যেসমস্ত কথা হীন, গ্রাম্য, সাধারণ, অনার্যোচিত, অনর্থযুক্ত যাহা নির্বেদের অভিমুখে, বিরাগের অভিমুখে, নিরোধের অভিমুখে, উপশমের অভিমুখে, অভিজ্ঞার অভিমুখে, সম্বোধির অভিমুখে, নির্বাণের অভিমুখে, সংবর্তিত হয় না; যথা : রাজকথা, চোরকথা, মহামাত্যকথা, সেনাকথা, ভয়কথা, যুদ্ধকথা, অন্নকথা, পানকথা, বস্ত্রকথা, শয়নকথা, মাল্যকথা, গন্ধকথা, জ্ঞাতিকথা, যানকথা, গ্রামকথা, নিগমকথা, নগরকথা, জনপদকথা, স্ত্রীকথা, শূরকথা, বিশিখা (রাস্তাবাসী) কথা, কুম্ভস্থান (জলঘাটে কুম্ভদাসীদের) কথা, পূর্বপ্রেত কথা, নানাত্বকথা, লোক-আখ্যায়িকা, সমুদ্র-আখ্যায়িকা, ইতি ভবাভব (এরূপ হইয়াছে বা এরূপ হয় নাই) কথা ইত্যাদি এইরূপ কথা বলিব না। এইরূপে তিনি সম্প্রজ্ঞাত হন। কিন্তু, আনন্দ, যেসমস্ত কথা কঠোরভাবে সংযত এবং

চেতভাবনোযোগী যাহা সম্পূর্ণরূপে নির্বেদের অভিমুখে... সংবর্তিত হয় যথা: অল্পেচ্ছাকথা, সন্তুষ্টিকথা, প্রবিবেককথা, অসংসর্গকথা, বীর্যারম্ভকথা, শীলকথা, সমাধিকথা, প্রজ্ঞাকথা, বিমুক্তিকথা, বিমুক্তিজ্ঞানদর্শনকথা, ইত্যাদি, এইরূপ কথা বলিব। এইরূপে তিনি সম্প্রজ্ঞাত হন। যদি সেই ভিক্ষুর এইরূপে অবস্থানের সময় এইরূপ বিতর্কের জন্য চিত্ত নমিত হয়: যে-সকল বিতর্ক হীন, গ্রাম্য... সংবর্তিত হয়; যথা : কামবিতর্ক, ব্যাপাদবিতর্ক, বিহিংসাবিতর্ক ইত্যাদি বিতর্কে আমি বিতর্ক করিব না, এইরূপে তিনি সম্প্রজ্ঞাত হন। যে-সকল বিতর্ক আর্যোচিত, মুক্তি অনুযায়ী যাহা তদনুবর্তী ব্যক্তির পক্ষে সম্যকভাবে দুঃখক্ষয়ের উপায় হয়; যথা : নৈষ্ক্রম্যবিতর্ক, অব্যাপাদবিতর্ক, অবিহিংসাবিতর্ক ইত্যাদি বিতর্কে আমি বিতর্ক করিব—এইরূপে তিনি সম্প্রজ্ঞাত হন।

আনন্দ, এই সকল পঞ্চ কামগুণ। কী কী পঞ্চ? চক্ষুবিজ্ঞেয় রূপ ইষ্ট, কান্ত, মনোজ্ঞ, প্রিয়রূপ, কামসংযুক্ত, মনোরঞ্জক। শ্রোত্রবিজ্ঞেয় শব্দ, ঘ্রাণবিজ্ঞেয় গন্ধ, জিহ্বাবিজ্ঞেয় রস, কায়বিজ্ঞেয় স্প্রষ্টব্য ইষ্ট... মনোরঞ্জক—এই সকল পঞ্চ কামগুণ। আনন্দ, ভিক্ষুর অভিক্ষণ (সতত) স্বীয় চিত্তে এরূপ প্রত্যবেক্ষণ করা উচিত: আমার চিত্তে কি এই সকল পঞ্চ কামগুণের কোনো একটির আয়তন সমুদাচার উৎপন্ন হয়? যদি, আনন্দ, প্রত্যবেক্ষণকালে ভিক্ষু প্রকৃষ্টরূপে জানেন: আমার চিত্তে... উৎপন্ন হয়, এইরূপ হইলে ভিক্ষু প্রকৃষ্টরূপে জানেন—পঞ্চ কামগুণে যে ছন্দরাগ, তাহা আমার মধ্যে প্রহীন হয় নাই। এইরূপে তিনি সম্প্রজ্ঞাত হন। যদি, আনন্দ, প্রত্যবেক্ষণকালে তিনি এইরূপ প্রকৃষ্টরূপে জানেন—আমার চিত্তে... উৎপন্ন হয় না, এইরূপ হইলে ভিক্ষু জানেন: আমার মধ্যে... প্রহীন হইয়াছে; এইরূপে তিনি সম্প্রজ্ঞাত হন।

আনন্দ, এই পঞ্চ উপাদান-স্কন্ধ যাহাতে ভিক্ষুর উদয়-ব্যয়ানুদর্শী হইয়া অবস্থান করা উচিত। ইহা রূপ, ইহা রূপের সমুদয়, ইহা রূপের অস্তগমন। বেদনা, সংজ্ঞা, সংস্কার, বিজ্ঞান সম্পর্কেও এইরূপ। তাঁহার এই পঞ্চ উপাদান-স্কন্ধে উদয়-ব্যয়ানুদর্শী হইয়া অবস্থানহেতু পঞ্চ উপাদান-স্কন্ধে 'আমি আছি' যে অভিমান, তাহা পরিত্যাগ করেন। এইরূপ হইলে ভিক্ষু প্রকৃষ্টরূপে জানেন: পঞ্চ উপাদান-স্কন্ধে আমার 'আমি আছি' যে অভিমান, তাহা পরিত্যক্ত হইয়াছে—তিনি এইরূপে সম্প্রজ্ঞাত হন। আনন্দ, এই ধর্ম সম্পূর্ণরূপে কুশলোদ্ভুত, আর্য (নির্দোষ), লোকোত্তর ও পাপমুক্ত।

আনন্দ, তুমি কী মনে করো? কি উপকারিতা দেখিয়া শিষ্য শাস্তাকে

অনুসরণ করা উচিত মনে করে? ভদন্ত, আমাদের ধর্ম ভগবান-মূলক, ভগবান পরিচালিত ও ভগবান আশ্রিত। সাধু, ভদন্ত, ভগবান সম্পর্কে এই ভাষণের অর্থ প্রকাশ করুন। ভগবানের নিকট হইতে ভিক্ষুগণ অবধারণ করিবেন।

আনন্দ, সূত্র ও গেয়্য বিশ্লেষণের জন্য শাস্তাকে অনুসরণ করা শিষ্যের উচিত নয়। তাহা কী হেতু? আনন্দ, দীর্ঘকাল ধরিয়া ধর্মশ্রুত, (সুন্দররূপে) ধৃত, আবৃত্তি দ্বারা সুপরিচিত, মনন দ্বারা অনুবীক্ষিত এবং প্রজ্ঞার দ্বারা সুপ্রতিবিদ্ধ। যে-সকল কথা কঠোরভাবে সংযত... বিমুক্তিজ্ঞান দর্শন কথা এইরূপ কথার জন্য শাস্তাকে অনুসরণ করা শিষ্যের পক্ষে উপযোগী।

আনন্দ, এইরূপ হইলে আচার্যের পক্ষে উপদ্রব, অন্তেবাসীর পক্ষে উপদ্রব, ব্রহ্মচর্যের পক্ষে উপদ্রব হয়। কিরূপে আচার্যের পক্ষে উপদ্রব হয়? কোনো শাস্তা নির্জন শয়নাসন (বাসস্থান) ভজনা করেন; যথা : অরণ্য, বৃক্ষমূল, পর্বত, কন্দর, গিরিগুহা, শ্মশান, বনখণ্ড, উন্মুক্ত প্রান্তর ও পলালপুঞ্জ। তাহার ব্যপকৃষ্ট (বিবিক্ত) হইয়া অবস্থানকালে ব্রাহ্মণ গৃহপতি, নিগমবাসী ও জনপদবাসী তাঁহার চারিপাশে জড় হয়। উহাদের দ্বারা সমাবৃত হইলে তিনি মূর্ছিত (মোহিত), কামযুক্ত, ঈর্ষাপরায়ণ ও প্রাচুর্যের জন্য আবর্তিত হন। আনন্দ, ইহাকেই বলা হয় উপদ্রুত আচার্য। আচার্য-উপদ্রব হেতু সংক্লেশযুক্ত, পুনর্জন্মদায়ী, ভয়জনক, দুঃখবিপাকী, জন্ম-জরামরণ-পরিণামী পাপ ও অকুশলধর্ম তাঁহাতে আহত করে। এইরূপে আচার্য-উপদ্রব হয়। আনন্দ, কিরূপে অন্তেবাসী উপদ্রব হয়? সেই শাস্তার বিবেক (নির্জনবাস) অভ্যাস করিবার কালে নির্জন শয়নাসন ভজনা করেন; যথা : ... এইরূপে অন্তেবাসী উপদ্রব হয়।

আনন্দ, কিরূপে ব্রহ্মচর্য-উপদ্রব হয়? আনন্দ, তথাগত অর্হৎ সম্যকসম্বুদ্ধ, বিদ্যাচরণসম্পন্ন, সুগত, লোকবিদ, অনুত্তর পুরুষদম্য সারথি, দেবমনুষ্যের শাস্তা, বুদ্ধ, ভগবান এই পৃথিবীতে আবির্ভূত হন। তিনি বিবিক্ত শয়নাসন ভজনা... প্রাচুর্যের জন্য আবর্তিত হন না। কিন্তু এই আচার্যের শিষ্য... এইরূপে ব্রহ্মচর্য-উপদ্রব হয়।

আনন্দ, ইহাদের মধ্যে আচার্য উপদ্রব ও অন্তেবাসী উপদ্রব অপেক্ষা ব্রহ্মচর্য-উপদ্রব অধিকতর দুঃখ পরিণামী, কটুক পারিণামী এবং বিনিপাতের জন্য সংবর্তিত হয়। সুতরাং তোমরা আমার প্রতি মিত্রবৎ আচরণ করো, শত্রুবৎ নহে, ইহা তোমাদের পক্ষে দীর্ঘকাল হিত ও সুখের কারণ ইহবে। আনন্দ, কিরূপে শিষ্যগণ শাস্তার প্রতি শত্রুবৎ আচরণ করে, মিত্রবৎ নহে? এইস্থলে অনুকম্পা হিতৈষী শাস্তা অনুকম্পাপূর্বক শিষ্যদের ধর্মদেশনা

করেন : ইহা তোমাদের হিতের জন্য, ইহা তোমাদের সুখের জন্য। কিন্তু তাঁহার শিষ্যগণ মনোযোগ-সহকারে শোনেন না, কর্ণপাত করেন না। অন্য বিষয়ে চিত্ত-উপস্থাপিত করেন এবং শাস্তার অনুশাসন হইতে দূরে সরিয়া যান। এইরূপে তাঁহার শিষ্যগণ শত্রুবৎ... নহে। আনন্দ, কিরূপে শাস্তার শিষ্যগণ মিত্রবৎ আচরণ করেন, শত্রুবৎ নহে? এইস্থলে অনুকম্পাকারী... দূরে সরিয়া যান না। এইরূপে তাঁহার শিষ্যগণ... নহে।

সেইজন্য তোমরা আমার প্রতি... সুখের কারণ হইবে। আনন্দ, আমি তোমাদের প্রতি সেইরূপ পরাক্রম প্রদর্শন করিব না যেইরূপ একজন কুম্ভকার অদগ্ধ, অশুষ্ক মৃৎপাত্রে করিয়া থাকে। আমি নিরন্তর নিগ্রহ করিয়া মালিন্য দূর করিয়া কথা বলিব। যাহা সারবান তাহা স্থায়ী হইবে।

ভগবান ইহা বলিলেন। আয়ুষ্মান আনন্দ সন্তুষ্ট মনে ভগবানের ভাষণে আনন্দ প্রকাশ করিলেন।

মহাশূন্যতা সূত্র সমাপ্ত

৩. আশ্চর্য-অদ্ভুতধর্ম সূত্র[১]

আমি এইরূপ শুনিয়াছি।

এক সময় ভগবান শ্রাবস্তী-সমীপে জেতবনে অনাথপিণ্ডিকের আরামে অবস্থান করিতেছিলেন। সেই সময় বহু ভিক্ষু ভিক্ষাচর্যা হইতে প্রত্যাবর্তন করিয়া ভোজনান্তে উপস্থানশালায়[২] সমাবেত হইয়া এই কথা আলোচনা করিতেছিলেন, আশ্চর্য! বন্ধুগণ, অদ্ভূত! বন্ধুগণ, তথাগতের কী মহিমা, কী মহানুভবতা, যেহেতু তথাগত, অতীতের বুদ্ধগণ যাঁহারা পরিনির্বাণপ্রাপ্ত, ছিন্নপ্রপঞ্চ, ছিন্নাবর্ত[৩], কর্মাবর্ত, ক্ষয়সাধক ও সর্বদুঃখমুক্ত হইয়াছেন, তাঁহাদের জানিতে পারেন—ওই সকল ভগবান এই এই জাতি হইতে উদ্ভূত, এই এই নাম ও গোত্রযুক্ত। এইরূপ শীল ও ধর্মসম্পন্ন, এইরূপ প্রজ্ঞা... এইরূপ তাঁহাদের জীবনযাত্রা প্রণালি, এইরূপে বিমুক্ত ছিলেন। এইরূপ কথিত হইলে আয়ুষ্মান আনন্দ সেই ভিক্ষুদিগকে বলিলেন, বন্ধুগণ, ইহা আশ্চর্য ও অদ্ভুত যে তথাগতগণ আশ্চর্য ও অদ্ভুতধর্ম সমন্বাগত ছিলেন।

সেই ভিক্ষুদের এই আলোচ্য কথা বাধাপ্রাপ্ত হয়। ভগবান সায়াহ্নে সমাধি

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[১]। এই সূত্রটি দীর্ঘনিকায়ের মহাপদান সূত্রের অন্তর্ভুক্ত আছে।

[২]। সভাকক্ষ।

[৩]। কুশল-অকুশলকর্মের আবর্ত—প.সূ.

Chapter 2
The Neuroanatomy of Emotions

Abstract Common to many mammalians, the limbic system is a set of anatomical structures involved in emotions. Theorized in the last century by Papez and Mc Lean, this system includes the prefrontal cortex—where emotions access consciousness—as well as the hippocampus, amygdala, and hypothalamus. The hypothalamus and its extension, the pituitary gland, causes the visceral manifestations associated with these emotions. These emotional manifestations can be triggered by consciousness, but inversely, physical states can be made conscious thanks in part to the insula. The regulation of these emotional responses is also accomplished by subcortical structures: the basal ganglia. These nuclei—composed of the thalamus, striatum, globus pallidus as well as the subthalamic and accumbens nuclei—are linked to the cortex by loop circuits. These loops act as interfaces between the different components—emotional, cognitive, and motor—of our behavior.

> Man should know that joy, fun, laughter and entertainment, grief, sorrow and tears of discouragement can only come from the brain […]. This is because the same body as you can go crazy and insane and that the fear and anxiety attack us. All this happens when the brain is sick. I believe that the brain has the greatest power of man.
>
> *The Sacred Disease*, *Hippocrates*, 460–377 *av* [1].

In this excerpt, the father of medicine postulates that the ills of the mind are also those of the brain. Sigmund Freud was convinced that some of his psychoanalytical concepts would later be proven by advances in biology and anatomy: "we must remember that all our provisional ideas in psychology will probably 1 day be based on an organic infrastructure" [2]. Eight years later, in 1920, the Austrian neurologist added that: *the shortcomings of our description probably would fade if we could already establish physiological or chemical terms instead of psychological terms* [2]. Yet, rather than working side-by-side, psychoanalysis and neurobiology have often been at odds due to differing logics. Understanding psychiatry, and presumably psychosurgery, requires a detour through neuroanatomy including the neuroanatomy of emotions. But emotions have long been neglected by anatomists, probably in part because they lend themselves less easily to animal research.

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As Cabanis succinctly expressed, the brain *secretes thought as the liver secretes bile* [3]. The philosopher and physiologist might have added that the brain colors thoughts with emotions just as bilirubin gives bile its yellowish hue. This emotional component opens us to the joys and tragedies of life, but it is also involved—much more than we think—in our cognitive processes and decision-making.[1] Over the past 60 years, thanks notably to the results of psychosurgery, the development of functional neuroimaging[2] and advances in neurobiology, more has become known about the anatomical structures involved in emotional processes. These structures are regrouped in the *limbic system*, a term coined by the neurologist Paul Broca, from the latin *limbus* meaning "border," to designate the area surrounding the cerebral cortex [4]. Broca attributed our animalistic behavior to this entity, *the great limbic lobe*, as opposed to our nobler intellectual abilities, which seemed to arise in the cortex. The notion of a brain structure devoted to emotions, a limbic system, was most actively put forward in the late 1930s by Papez, and Mac Lean [5, 6]. To the cingulate cortex[3] and hippocampus[4] of the limbic lobe, they added the amygdala[5] and hypothalamus.[6] The prefrontal cortex,[7] central gray nuclei[8] and insula[9] later also joined the machinery of emotions, adding to an increasingly improbable list where *everything is connected to everything,* as neuroanatomists are fond of saying [7]. Our emotional manifestations, whether behavioral, autonomic, or cognitive, are thus supported by a diffuse system which itself interfaces with a great number of other brain functions, such as motor skills,

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[1] Concepts developed in the work of António Damásio, Californian neurologist, in particular in his book "Descartes' Error: Emotion, Reason and the Human Brain" Odile Jacob, Paris.

[2] For about 30 years new noninvasive technologies have given the possibility of an increasingly detailed mapping of the brain's activity. Thanks to these maps, we have "emotional activation" models, which show activity in brain structures related to different emotions. This is accomplished by external induction (exposing the subject to a stimulus triggering an emotion, like giggling or shocking images) or by internal induction (a depressed patient or a subject suffering painful memories). New imaging technologies include:

- TEP-scan, which uses positron emission. After injection of radioactive glucose, which becomes metabolized by certain brain areas, sensors can identify the activated areas in the subject's brain. The resolution of these images remains relatively coarse.
- Functional MRI (fMRI) is a type of imaging by magnetic resonance that allows visualization of the brain's blood flow in precise areas. The BOLD effect (Blood Oxygen Level Dependant), related to the magnetization of the haemoglobin in red blood cells, reveals which brain areas are being activated.
- Magnetoencephalography (MEG)

[3] Cf. p. 95.

[4] Cf. p. 103.

[5] Cf. p. 98.

[6] Cf. p. 112.

[7] Cf. p. 90.

[8] Cf. p. 122.

[9] Cf. p. 107.

cognition, or the senses. These latter functions will not be addressed herein. We will limit ourselves to detailing the pathways and structures relevant to psychosurgery.

The Organs of Emotion

Let us set the scene: the brain includes the cerebrum, the cerebellum, and brainstem. All three are contained in the skull and entirely enveloped by meninges. The meninges cover all the nerve tissue and are composed from outside to inside by the dura mater, the arachnoid mater, and the pia mater. In between these last two structures, blood vessels and cerebrospinal fluid (CSF) circulate. This fluid also flows into the brain through four cavities called ventricles. The cerebrum is composed of two hemispheres whose surfaces form the cortex and whose interiors, broadly speaking, form the thalami, basal ganglia, and the hypothalamic-pituitary axis.

The Cerebral Cortex

Abstract The cerebral cortex is the substrate in which consciousness as well as memory, language, and our perceptions take root. Of these two square meters of gray matter folded up against the walls of our skull, three lobes are heavily involved in emotions: the frontal, temporal, and insular lobes. The front of the frontal lobe, the dorsolateral cortex, is involved in the planning of behavior while the orbitofrontal cortex, closer to the middle, is involved in motivation. In the interior, the anterior cingulate cortex is involved in emotional processes. These three regions are each connected to basal ganglia, forming cognitive, and limbic loops. This prefrontal cortex, responsible for a large part of our cognitive processes—and abundantly connected to the rest of the limbic system—is part of the interface between cognition and emotion. The interior face of the temporal lobe shelters the hippocampus and the amygdala. The latter is where information from our senses converges. Depending on the situation, the amygdala will lend this sensory input an innate or acquired charge, such as fear, which the hypothalamus will then convert into autonomic manifestations. Researchers now believe the hippocampus plays a less essential role in emotions but that it is critical to memory. The insula, in turn, is used to analyze changes in our visceral states associated with emotional experience allowing us to consciously perceive this physical state.

The cerebral cortex—meaning "bark" in Latin—is a mantle of gray matter. This gray matter, famously synonymous with intelligence is composed of nerve cells

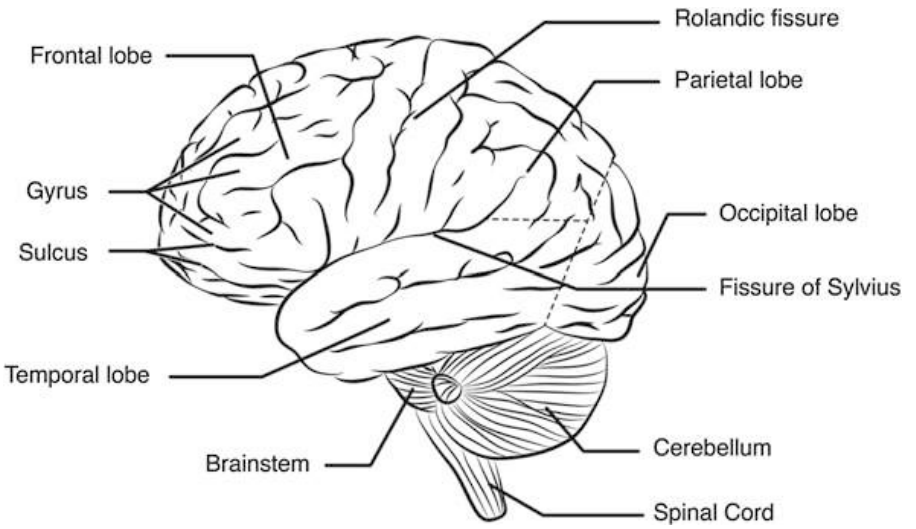

Fig. 2.1 Side view of the brain

called neurons. These cells have a projection, the axon, which allows them to connect to each other and form a network. The folds in the cortex, which greatly increase its surface area, are formed of *gyri*, (Latin *ridges*, sg. *Gyrus),* surrounded by *sulc*i, (Latin: "furrows", sg. *sulcus*). The deeper furrows which delineate the lobes are called fissures. In general, these fissures vary little from one individual to another. For example, the central, or Rolando's, separates between the frontal lobe, in front and the parietal lobe, in back. The lateral, or Sylvian fissure, divides the temporal lobe (Fig. 2.1).

At the bottom of this fissure is buried the smallest of the lobes, the insula, meaning "island" in Latin (Fig. 2.9, p. 64). The fifth lobe, the occipital lobe, located behind the temporal and parietal lobes, is less clearly demarcated. Within each of these lobes, specific areas called functional areas are devoted to specific functions. Lesioning or destruction of any given area from trauma, tumoral compression, or ischemia causes alteration or loss of that function. In fact, such lesions are what allowed brain functions to be mapped over the centuries. In the early 1950s, researchers, including Montreal neurosurgeon William Penfield, performed experiments on conscious patients in which electrical stimulation of the cerebral cortex triggered certain movements or behaviors and epileptic episodes. These experiments helped further refine the connections between certain functions and areas. They followed on work undertaken half a century earlier by the German neurologist Korbinian Brodmann who had compiled a meticulous survey of these functional areas and assigned each a number. His system is still used today: the numbered Brodmann areas. Now that the stage has been set, we will hereafter emphasize those anatomical structures directly relevant to our subject because of their essential role in emotional processes: the frontal and temporal lobes.

The Frontal Lobe

In 1861, Paul Broca, a neurologist at the Salpêtrière Hospital in Paris, was the first to show through clinical observations combined with subsequent autopsies the important role of the lower, posterior part of the left frontal lobe in articulated language in Genuinely right-handed subjects. This region, areas 44 and 45, according to Brodmann's classification, was named, *Broca's area.* The most posterior part of the lobe, located directly ahead of the central or Sylvian fissure, is the primary motor cortex (area 4). In front of this is the pre-motor area (area 6), which helps plan movements, and ahead of it is area 8, which is responsible for eye movements. The voluminous area in front of the motor region representing almost one-third of the cortical mass is called the *prefrontal cortex*. It is intimately linked with cognitive and emotional processes. Connected to many parts of the brain, the prefrontal cortex receives sensory information already processed in the so-called *associative* regions of the occipital temporal or parietal cortex. Visual information, an image captured by the retina, for example, is transmitted along the primary visual pathway to the occipital cortex, which receives it in "raw" form. The occipital associative cortex is where the various elements composing this "visual stream" transmitted by the primary cortex are recognized and labeled. The same occurs for auditory information in the temporal associative cortex, which among other things, converts sounds into words. The parietal associative cortex, meanwhile, is involved in interpreting tactile information. In addition to being connected to these associative areas, the prefrontal cortex is tightly linked to the rest of the limbic system: the hippocampus, amygdala, hypothalamus, and thalamus especially the dorsal medial nucleus of the thalamus (Fig. 2.2).

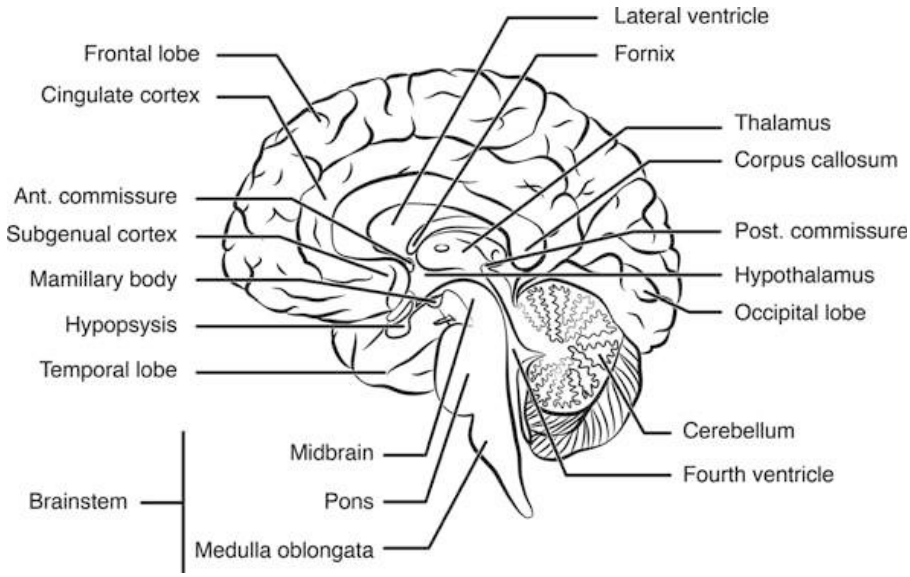

Fig. 2.2 Medial view of the brain

Additionally, there are projections leading toward the basal ganglia and in particular the striatum. These projections are actually part of loops, since once projected onto the striatum and then the pallidum, the information is sent onto the thalamus and from there back to its starting point, the prefrontal cortex. Before discussing,[10] the various cortico-striato-thalamo-cortical (CSCT) loops involved in cognitive functions and the regulation of emotions, the three regions which form the prefrontal cortex must be described: the dorsolateral, orbitofrontal, and cingulate cortices.

The Dorsolateral Cortex

The dorsolateral region of the prefrontal cortex (areas 9, 10 lateral and 46) (Fig. 2.3) is intimately linked to the rest of the prefrontal cortex and to the dorsomedial and ventral anterior nuclei of the thalamus.[11] It extends over the dorsolateral region of the caudate nucleus[12] and is implicated in the *associative*[13] loop (Fig. 2.27, p. 89) [8]. This cortex is involved in tasks requiring spatial memory, concentration, planning, problem solving and the acquisition of rules [9]. In their clinical practice, neuropsychologists call these the *executive functions*" [10]. In a way, they are also what philosophers have referred to as consciousness. As Bergson writes, *consciousness is anticipation of the future… a hyphen between what was and will be*" [11]. Selective lesions of this region cause changes in the executive functions, and inversely, functional imaging reveals activity in this cortex during tasks involving planning. This zone is also active when an individual is attempting to control certain negative emotions. In patients with severe depression, functional imaging studies show little activity in this cortex. Clinically, this translates to psychomotor retardation, including memory and attention disorders and apathy. On the contrary, an increase in activity can be observed in successfully treated patients [12, 13]. In depressive subjects, this dorsolateral cortex seems more active on the right than on the left [14, 15]. Today, repetitive transcranial magnetic stimulation (rTMS)[14] can be used to treat certain depressive patients who do not respond to drug-based treatments. Two protocols exist: either the left dorsolateral cortex can be "woken up" through high frequency rTMS or the right dorsolateral cortex can be inhibited through low-frequency rTMS. Clinical research protocols are currently attempting to determine whether the effect can be sustained over the long term through the implanting of cortical electrodes to maintain stimulation.[15] When a clinical improvement is achieved,

[10] Cf. p. 139.
[11] Cf. p. 123.
[12] Cf. p. 128.
[13] Cf. p. 141.
[14] Cf. Indications and principle of the rTMS p. 232.
[15] Cf. Indication and principle of the cortical stimulation p. 236.

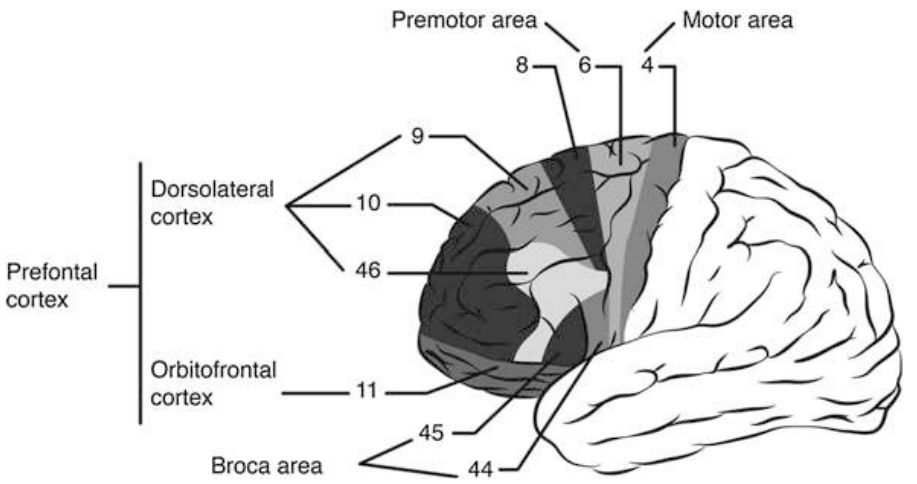

Fig. 2.3 The dorso-lateral prefrontal cortex

functional imaging shows a normalizing of the activity in this region as well as in the related anterior and subgenual cingulate cortex [16, 17].

The Orbitofrontal Cortex

This part of the brain, Brodmann areas 10 medial, 11, 12, and 47, (Fig. 2.4) is located against the skull and above the orbits. Like the dorsolateral cortex, the orbitofrontal cortex is tightly connected to the cingulate cortex, as well as the rest of the associative cortex, the amygdala, and the dorsomedial and ventral anterior nuclei of the thalamus [18]. This cortex projects onto the ventromedial part of the caudate nucleus [8] which is involved in the associative loop[16] and has the particularity of receiving information from all of our five senses [19]. This region and in particular its innermost *medial* part, is implicated in emotional and motivational processes, particularly those involving the notion of reward [20, 21]. Its role, as emphasized by the psychiatrist B. Aouizerate [22], is essential "*in the interpretation of sensory information from the environment by giving it meaning on an emotional and motivational level according the subject's previous experiences*," which will affect the decision-making process [21]. The lateral part of the cortex is involved in *cognitive*, tasks, mental processes requiring judgment, perseverance or the detection of errors [18]. The orbitofrontal cortex also regulates social behavior as the previously mentioned case of *Phineas Gage*[17] illustrated. Following an accident in which Gage suffered trauma to this part of the brain, he became antisocial, irresponsible, impulsive, and childish [23]. In general, focused lesions in this cortex inhibit the subject's ability to select an appropriate behavioral response based on

[16] Cf. p. 142.
[17] Cf. p. 25.

Fig. 2.4 The orbitofrontal (10, 11, and 12) and subgenual (25) cortices

social or emotional cues. Functional imaging reveals increased activity of this region of the cortex [12] in patients suffering from depression or OCD. Here too, normalization has been observed following effective treatment [12, 24–26].

The Anterior Cingulate Cortex

The cingulate gyrus,from *cingulum* meaning "belt" in Latin, wraps around the corpus callosum[18] in the medial part of both hemispheres (Fig. 2.4). As with the orbitofrontal cortex, this cortical area is involved in various motivational, emotional, or cognitive processes, such as attention, working memory, error detection [27], managing conflict situations, and anticipation. The cingulate cortex, particularly its anterior part (areas 24, 32, and 25) (Fig. 2.5), is closely linked to the insula,[19] another structure involved in emotions. According to Damasio, when we experience emotions, "the insula has both a sensorial and motor function though it is focused more on the sensorial aspect of the process, while the anterior cingulate operates as the motor structure" [28]. The anterior cingulate cortex (ACC) is reciprocally linked to the dorsomedial nucleus of the thalamus. The anterior part of the gyrus projects its fibers toward the amygdala, which it holds in check, toward the peri-acqueducale gray matter[20] as well as toward the ventral striatum and nucleus accumbens,[21] thus participating in a *limbic loop*[22] (Fig. 2.28, p. 91) [8].

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[18] The corpus callosum is a bundle of axons that connect both cerebral hemispheres. It assures the transfer of information between both hemispheres and their coordination (Fig. 2.2, p. 53).

[19] Cf. p. 107.

[20] The periaqueductal gray matter is situated in the midbrain's center around the Sylvius acqueduct connecting the third and the fourth ventricles. This gray substance plays an important role in pain control and defensive behaviors.

[21] Cf. p. 129.

[22] Cf. functional anatomy p. 143.

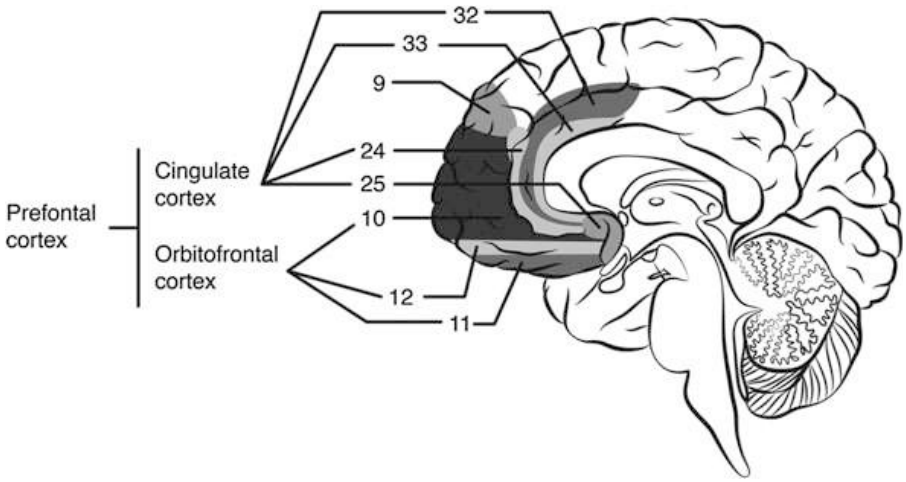

Fig. 2.5 The anterior cingulate and orbitofrontal cortices

These projections are involved in emotional and autonomic responses. Functional imaging reveals increased activity of the cingulate cortex in patients with OCD [12], particularly when these patients undertake tasks in which they must detect errors [22, 27]. A similar hyperactivity has also been noted in its most rostral part, the subgenual area (area 25), in patients with severe depression [29]. As will be discussed in a later section,[23] this finding is what originally led to deep brain stimulation being used during treatment of depressed patients. Significantly, this activity decreases when the depression is successfully treated. Moreover, the presence of such lively activity in the cingulate is a good indicator for the success of a cingulotomy,[24] another psychosurgical procedure used in the treatment of depression and OCD [30].

The Temporal Lobe

Abstract On its inner surface, the temporal lobe is in contact with the hippocampus and the amygdala. All sensory information from the various senses converges on the latter, and depending on the context the amygdala gives it emotional significance—innate or acquired—causing an autonomic response. It is involved in processing the social signals for emotions, especially fear, and the consolidation of emotional memories. By identifying hazards, it plays a fundamental role in preserving the individual. The hippocampus, located further back, places the event back into context and determines the conditions for forming a memory.

[23] Cf. p. 334.

[24] Cf. Technique's details p. 285.

The prefrontal cortex then participates in the analysis of these emotional events contrasting the present experience with past ones in order to reach a decision.

This lobe is located underneath the temporal bone, so named because the hairs on the *temples* are the first to suffer the ravages of time (Or in Latin *tempus*) and become gray. The temporal lobe, especially its inner region composed of the amygdala and hippocampus is also involved in many cognitive and emotional processes. In 1937, two American researchers, Klüver and Bucy, observed that primates that underwent bilateral removal of the inner portion of the temporal lobes suffered what they called *psychic blindness*: inability to grasp the emotional significance of sensory information, in particular visual information [31]. The monkeys no longer feared snakes or people and tried to mate with anyone within reach. This lack of discernment was also reflected on an oral level as the animals would try to put everything in their mouths. In addition to these sexual and feeding behaviors, the authors also observed significantly increased docility and placidity, resulting in a marked reduction in the subjects' social interactions [32].

The Amygdala

In 1956, new research on monkeys demonstrated that bilateral ablation centered, more exclusively this time, on the amygdala was enough to cause most of these symptoms [33]. Buried under the cortex, in the medial, anterior part of each temporal lobe, the amygdala takes its name from its almond shape (Fig. 2.6).

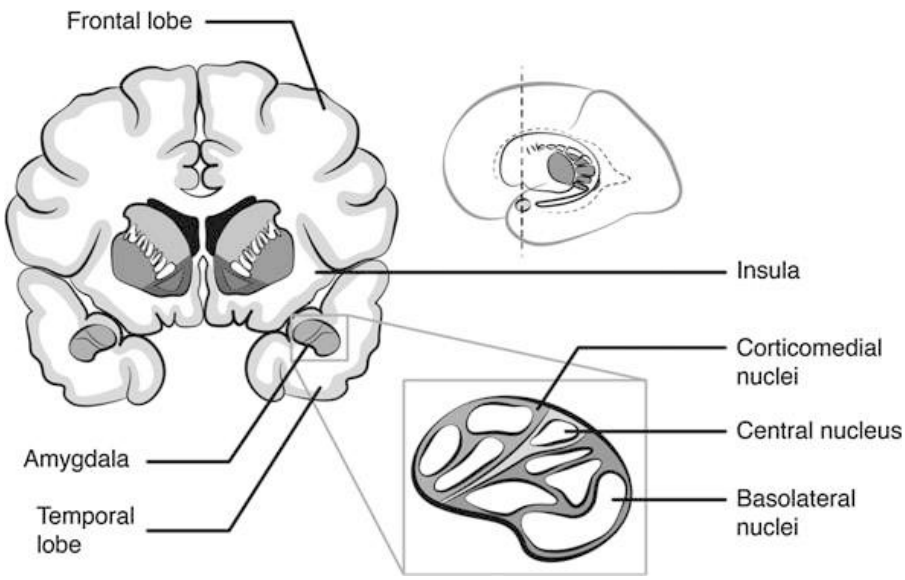

Fig. 2.6 The amygdala

Emotional processes all pass through, some may even arise in, the amygdala, which acts as a relay along numerous pathways. It receives information directly—or via the thalamus—from the associative cortical areas, the medial orbitofrontal cortex, the hippocampus, the basal ganglia, and septal nuclei (Fig. 2.7). After processing this information, the amygdala projects it—via the stria terminalis[25]—toward the hypothalamus[26] and other structures in the brainstem such as the locus coeruleus,[27] which is the source of autonomic and hormonal manifestations of certain emotions. As the neurologist Gil notes, "the amygdala is where the emotional component of the information conveyed by the sensory and sense pathways is integrated, and in conjunction with memory, where meaning is identified and biological and behavioral responses are modulated" [34]. The amygdaloid complex, through its connections, is composed of three nuclei groups. The corticomedial nuclei receive information from the olfactory bulb and project toward the hypothalamus. The basolateral nuclei, receive information from the associative

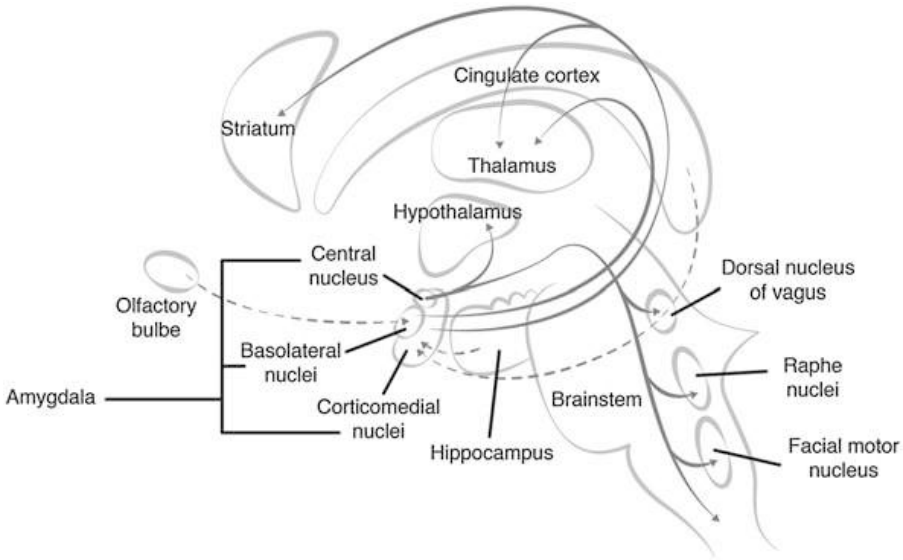

Fig. 2.7 The connections of the amygdala nuclei

[25] The stria terminalis runs in a trajectory parallel to fornix's from the amygdala to the hypothalamus, the septal area and passes over the "bed nucleus of the stris terminalis," a group of neurons directly behind the anterior commissure. This bundle of neurons is usually considered an extension of the amygdala, and more precisely of its central nucleus, for histological reasons and because of its multiple connections with the hypothalamus, the brainstem nuclei and in particular the ventral tegmental area (VTA). Its activity also seems modulated by the orbifrontal cortex. This structure has attracted the attention of an increasing number of researchers. It occupies a strategic anatomical position which enables regulation of the stress and reward centers.

This nucleus actually projects to one of the major reward centers (the VTA) and to the hypothalamic paraventricular nucleus (p. 112), which is essential to the activation of the corticotropic axis (p. 146).

[26] Cf. p. 112.

[27] Cf. Norepinephrin and the stress circuit p. 150.

sensory cortex and hippocampus and project toward the ventral striatum ventral, accumbens nucleus, and the dorsal medial nucleus of the thalamus.[28] Finally, the central nucleus, which is connected to the associative sensory areas through its links with the basolateral and cortico medial nuclei, receives information on the visual, auditory, tactile, and olfactory environment of the individual [35]. This nucleus sends information onto the hypothalamus and brainstem where the dorsal nucleus of the vagus nerve[29]—the source of parasympathetic responses—is located. From there information travels to the motor nuclei of the facial muscles—responsible for facial expression of emotions—the raphe nuclei,[30] the locus cœruleus[31] and nucleus basalis of Meynert.[32] These last three anatomical structures are, respectively, the source of serotoninergic,[33] noradrenergic[34] and cholinergic responses, three neurotransmitters at the heart of emotional processes. At the level of the unconscious, the amygdala sorts this information in terms of the danger it may pose the individual. Its role is therefore crucial in the phenomena of fear and anxiety.[35]

The amygdala contributes to emotional experience—positive or negative—according to the situations and the environment. The sensory and associative *cortex* and the *olfactory bulb* inform the *basolateral complex* and the *cortical* and *medial nuclei* about the environment, related to the memory (*hippocampus*). This information is integrated and transmitted to the *central nucleus* which will produce an emotional response: the *facial motor nucleus* will provoke fear or disgust, the *dorsal nucleus of the vagus nerve* and the hypothalamus will provoke respectively a parasympatic or sympatic response. The *raphe nucleus* will activate a serotonergic stimulation of the encephalus. The basolateral nuclei take action in motivational behaviour through the *ventral striatum* and the orbifrontal cortex.

This implicit, subcortical processing of information, "I act and then I think" lowers the response time necessary for protective behavior by eliminating the need for the information to pass through the cortex [36]. If sensory data conveys a threat, real or imagined, then the connections between the central nucleus of the amygdala and the hypothalamus and brainstem are activated and the individual responds with a series of autonomic reactions: quickening of the pulse, dilation of the pupils, draining of color from the face, and various hormonal responses. These phenomena prime the body for a *fight or flight*, response, according to physiologist Cannon [37].

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[28] Cf. p. 124.

[29] Details of the vagus nerve and its electrical stimulation in depression treatment. Cf. p. 241.

[30] Serotonin producing nucleus cf. p. 149.

[31] Ibid.

[32] In 2008, after a electrode trajectory error, an Italian team recorded the appearance of depression in a dystonia patient following stimulation of this area. This depressive state disappeared after repositioning of the electrode [214].

[33] Cf. p. 149.

[34] Ibid.

[35] Drugs in the benzodiazepine family, like Diazepam(r)®, decrease fear and anxiety responses because the amygdala is rich in receptors for this type of molecule. Efficacy is maintained even after removal of the amygdalae because similar receptors are located in other areas as well.

For example, the sudden appearance of a snake will trigger a biological response putting the organism on high alert and "doping it" in order for it to face the danger or make an escape. The amygdala therefore appears crucial to the preservation of the organism by allowing organisms to identify danger.[36] The detection of danger also occurs more subtly when, for example, an individual reads an expression of fear on someone else's face.[37] Direct electrical stimulation of the amygdala—or seizures, which can be likened to the cortex stimulating itself—produces reactions similar to those displayed when faced with danger. Additionally, these events are often associated with aggressiveness or a feeling of *déjà vu*. In contrast, pathological or surgical destruction of this structure, in addition to inhibiting the expression of fear and the recognition of fear on others' faces, reduces aggressive behavior [38, 39]. Acts of violence or aggression may, therefore, be linked to an imbalance caused by improper prefrontal modulation and amygdala hyperactivity [40]. To test this hypothesis, in the 1960s Narabayashi performed bilateral amygdalotomies in 60 patients with severe aggressive behavior [41, 42]. The Japanese neurosurgeon reported significant improvement in 85 % of the patients. These results are similar to those achieved with hypothalamotomies, another procedure with the same indication, which we will return to later.[38] These two techniques which were practiced until the late 1980s [43–48], have now almost completely disappeared. This decline stemmed from inadequate long-term monitoring, advances in pharmacology and, especially, ethical questions raised by such interventions [49].

More generally, the amygdala contributes to the interpretation of all sensory information with emotional content [50]. Studies in patients with lesions in the amygdala have also shown that this structure [51] intervenes both during the encoding of memories with emotional valence—positive or negative—as well as during recall[39] [52]. The amygdala is also involved (through reciprocal connections between its basolateral nuclei and the nucleus accumbens) when the reward circuit is solicited [53]. As such, it may be implicated in instances of relapse in cases of addiction[40] : the addict may be inclined to take the addictive substance once again when confronted with a situation previously associated with the substance [54].

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[36] In laboratory tests, the conditioned fear model allowed the role of the amygdala to be understood: a rat is placed in a wire lattice and a signal warns it before each electrical discharge. After multiple sessions, the rat shows signs of anxiety (immobilization, blood pressure increase). These signs disappear after elimination of the amygdalae (LeDoux J. E. 1998. The emotional brain: the mysterious underpinnings of emotional life. Simon & Schuster).

[37] For many years Damásio studied a 28-year-old patient suffering from a bilateral lesion of the amygdalae who was not able to recognize facial expressions like fear, surprise, or disgust.

[38] Cf. p. 364.

[39] An American study of veterans with severe head injuries showed that soldiers with amygdala lesions almost never develop post-traumatic stress disorder (PTSD). In contrast, other victims with this psychiatric disorder showed amygdalar hyperactivity [215]. These observations and animal experimentation data lead certain teams to consider cerebral stimulation of the amygdala as treatment for severe PTSD [216].

[40] Cf. Physiopatholog des addictions p. 359.

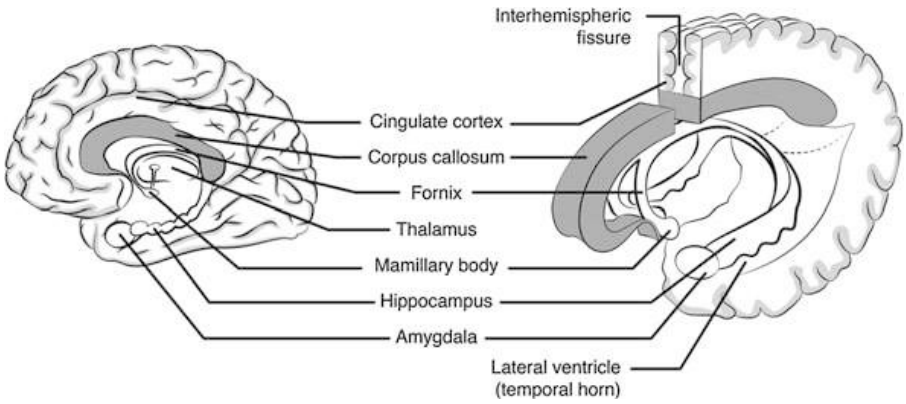

Fig. 2.8 The hippocampus and the hippocampal convolution

The Hippocampus

In behavior based on conditioning, the amygdala interacts closely with the hippocampus[41] a structure located just behind it (Fig. 2.8). Oblong in shape and presenting the appearance of a sea horse, from which it draws its name, this structure maintains close connections with the amygdala as well as with the rest of the associative cortex via the entorhinal cortex.[42] This region, which gathers the cortical information headed to the hippocampus, is also involved in spatial orientation [55]. The hippocampus extends back into the hippocampal gyrus and the fornix. The fibers of the fornix then rejoin the mammillary bodies.[43]

This set of structures plays a crucial role in the declarative memory formation process [56]. *Declarative* memory, refers to consciously accessible information which can be described through language: such as recollecting a history lesson, vocabulary skills (called *semantic* memory, from Greek *semantikos:* "meaning"), as well as remembering events in our life (called *episodic*). The hippocampus, which lies at the heart of the memory circuit (also called the *Papez circuit*[44]) acts as a repeater taking information quickly learned and passing it onto the rest of the cortical mantle, where long-term memory. Neurobiologist Vincent likens it to a mechanism for comparing *the state of the world to its emotional value. Nerve impulses travel around the hippocampal circuits rhythmically at a rate of* 50 *to* 100 Hz.

[41] To illustrate the complementarity of these structures Damásio gives the example of an individual without amygdalae but with his hippocampus intact who, although he remembered a traumatic event, did not show any fear when confronted with similar circumstances. In contrast, the neuroscientist presents another case of a patient without his hippocampus but with his amygdalae who experienced terror while not being able to remember the cause [217].

[42] This appears to be the first area affected by Alzheimer's disease.

[43] Cf. p. 112.

[44] Cf. Anatomic description of this circuit. p. 133.

This oscillating electrical activity plays an important part in the formation of memories; present during learning it reappears strongly during dreaming, incidentally showing the probable relationship between memory and dream [57]. Long-term memory storage occurs throughout the cortex. Semantic memory resides predominantly in the frontal and temporal cortex of the dominant hemisphere, while episodic memory utilizes more the frontal lobes[45] [58]. In addition to memorization, the hippocampus is also involved in the recall of stored memories. Recall can be initiated by the cortex in response to a cognitive process, but it can also be initiated directly in the olfactory pathway which is located very close to the hippocampus. *And as soon as I had recognized the taste of the piece of madeleine soaked in her decoction of lime-blossom which my aunt used to give me (although I did not yet know and must long postpone the discovery of why this memory made me so happy) immediately the old grey house upon the street*, […] and with the house the town, from morning to night and in all weathers, the Square where I used to be sent before lunch, the streets along which I used to run errands, the country roads we took when it was fine."[46] The powerful effect that the madeleine has on Proust clearly demonstrates the anatomical vicinity of the olfactory cortex and the hippocampus, but it also shows the close ties binding emotions to memory.[47] It seems that the hippocampus, particularly its posterior part, is also fundamental to spatial orientation. London taxi drivers are often cited to illustrate this as well as the phenomenon of brain plasticity. Imaging studies have shown that in these drivers the hippocampus is more developed than in the population at large because it is constantly being solicited [59]. Deep brain stimulation in the entorhinal cortex, the gateway to the hippocampus, may also increase spatial memory[48] [60]. Using a video game simulating a taxi in a virtual city, a California team recently demonstrated that stimulation of the entorhinal region of seven epileptic patients as they were learning the various routes was associated with improved recall. This is similar to work accomplished by Lozano, and his team on the stimulation of the fornix.[49] This type of research paves the way for neuroprostheses to treat memory decline observed in some neurodegenerative diseases such as Alzheimer's disease, which affects nearly 40 million people worldwide [61, 62].

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[45] To this conscious declarative memory at the cortex's surface is opposed the unconscious procedural memory of our abilities (like ridding a bicycle or playing piano) arising in structures like the basal ganglia or the cerebellum. Nonetheless, the connection between both systems and hence the passage from one memory form to the other remains permeable.

[46] Cf. Proust [218].

[47] Cf. Emotional memory p. 135.

[48] A team from Marseille, led by F. Bartholomei and P. Chauvel, observed in 2004 that electrical stimulation of the endonasal cortex provoked "déjà vu," i.e., the feeling of having already experienced something being experienced for the first time. In fact, stimulation of this cortex forces a process of recall in the hippocampus or the rhinencephalon (which also participates in memory encoding). Electrical stimulation or even epileptic seizures can provoke a simultaneous processes of encoding and recall giving the subject the impression of reliving a scene that is being experienced for the first time [219].

[49] Cf. p. 200: plasticity and neurogenesis resulting from DBS.

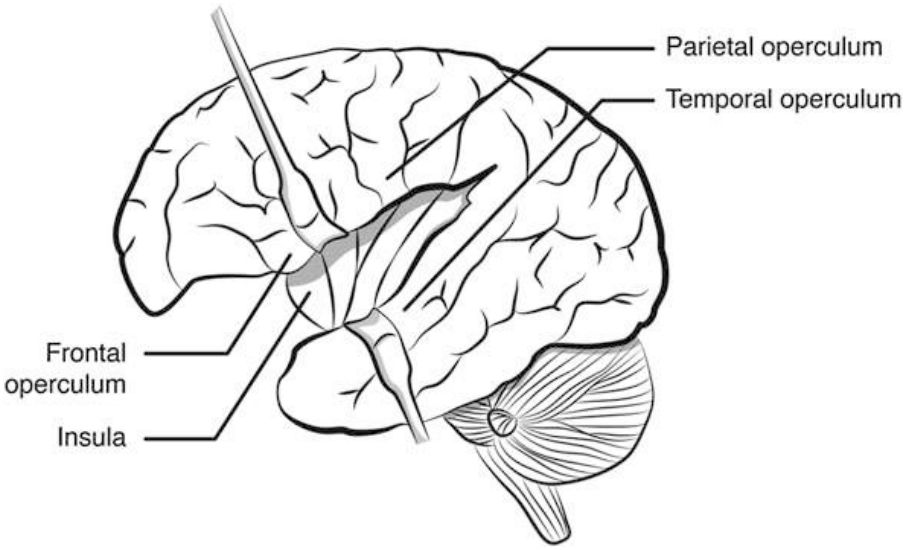

Fig. 2.9 Frontal and temporal lobes are drawn aside showing the insula

The Insula

The edges of the lateral furrow hide a deep depression in the folds of the cortex which contains a triangular lobe (Fig. 2.9). The insular cortex has five small circonvolutions. The cortex is involved in emotions and homeostatic regulation of the body. The anterior part of the insula receives projections directly from the central ventral thalamic nucleus and has reciprocal connections to the amygdala, while the posterior region connects to the associative somatosensory cortex and also receives thalamic afferents.[50]

The anterior portion, which is related to the senses of smell and taste, can trigger certain emotions such as disgust. This protective emotional reaction safeguards the individual against eating spoiled food which has become malodorous. Damasio goes further and considers that disgust—one of the oldest emotions to have evolved—triggered by the insula, may be relatively *developed and applicable to various situations in which the purity of objects or behaviors are compromised and where contamination exists.* [The subjects] *are disgusted by the perception of morally reprehensible actions.*. The Californian neurologist adds that, *the insula is an important correlate of all conceivable types of feelings, those emotions associated with those corresponding to all forms pleasure or pain caused by a*

[50] The ventral, posterior, inferior, and ventromedial nuclei of the thalamus in particular.

variety of stimuli—hear music you love it or hate it; see images we love, including erotic, be short of drugs and feel lack[51] [63]. The American neurologist devised what is known as the *somatic markers*: hypothesis. According to this hypothesis, the insula maps visceral states associated with emotional experiences and assigns each situation a positive or negative physical response. This mapping allows the brain to very quickly choose between different action scenarios. According to Damasio, these mechanisms reduce the strain on our cognitive processes and allow them to focus on solving the problems for which they are best suited [28]. This assumption is part of a larger theory called *embodied cognition*,[52] which holds that conscious thought cannot be separated from emotions and their physical manifestations. In other words, the amygdala converts some sensory information into somatic responses by sending signals to the autonomic nervous system and endocrine system, which regulate heart rate, perspiration, and hormone secretion. The insula in turn detects these physiological changes and makes the individual conscious[53] of them. As the neuroscientists Ansermet and Magistretti [64] explain, the insula should be seen as a *interoceptive relay in the nervous system that continuously informs the brain on the state of the body. A first loop circuit is thus closed allowing the brain to perceive the somatic state associated with the perception of an external stimulus. The fact that the amygdala and insula are both connected to the prefrontal cortex, which is involved in certain types of memory, allows a second circuit, the memory loop, to be closed: an individual need only recall the source event of the stimulus to again feel the associated physical sensations.* Clinical observations clearly reinforce this theory. For example, the higher up along the spinal cord a lesion is located, the duller the patient's emotional awareness grows due to a lack of autonomic afferents (Fig. 2.10) [65].

[51] Functional imaging studies showed lobe activation in drug-addicted subjects (cocaine, alcohol, opiates, and nicotine) exposed to environmental factors associated with their drug habits. Recent work showed that cigarette smokers with lobe damage lose practically all desire to smoke. It also revealed that these individuals were 136 times more likely to lose their tobacco addiction than smokers affected in other areas of the brain [220].

[52] "Embodied cognition."

[53] In some ways, this concept stating that changes in somatic perception modify the conscious perception of an emotion agrees with the "peripheral" theory of James and Langes, two psychologists during the nineteenth century who considered that emotion was a response to physiologic changes (trembling, accelerated cardiac rhythm…). The example of the cobra is often cited to illustrate this theory: the vegetative manifestation unconsciously provoked by the sight of the reptile, not its presence, provokes the fear response. Critics of James and Langes' theory explain that physiologic reaction times are too slow to be the source of sudden emotions and that the range of physiologic manifestations is too limited to portray all emotions. Cannon and Bard formulate the opposite hypothesis. According to their theory, emotional experience is at the origin of physiologic excitation.

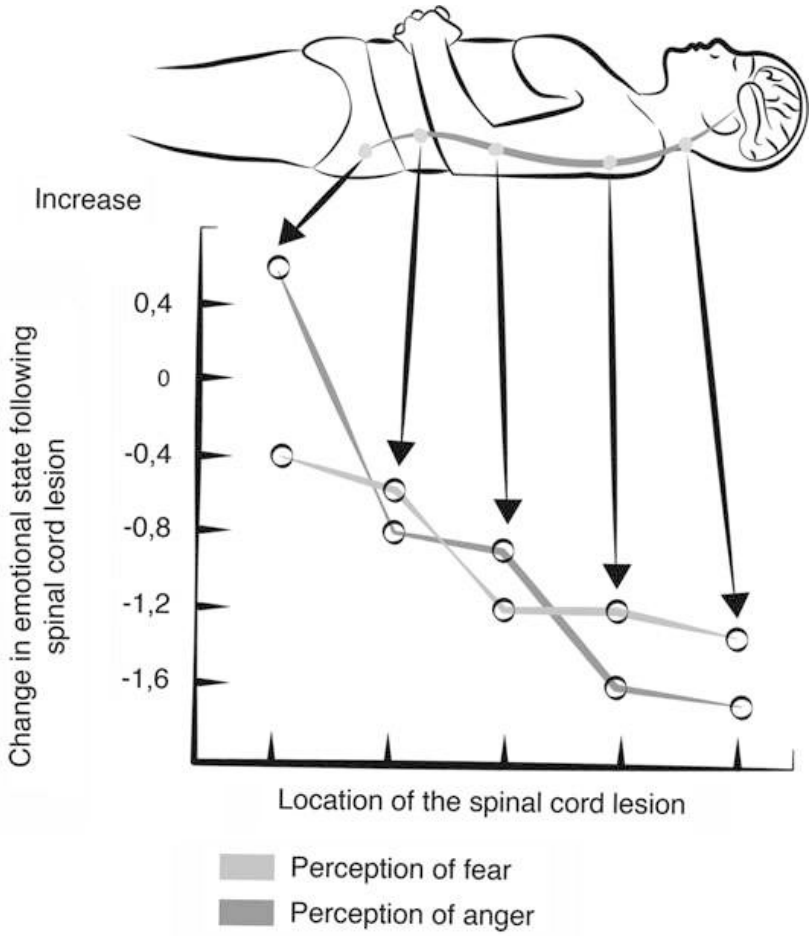

Fig. 2.10 Emotional experience of a person based on the degree of a medullary traumatism. The higher up along the spinal chord the lesion, the weaker the emotional experience, according to [68]

These data are confirmed by functional imaging, which reveals changes in prefrontal activity in these patients [66]. Some authors believe that this mechanism may come into play during the treatment of depression through stimulation of the vagus nerve.[54] By modifying the autonomic *return,* such stimulation may reduce the emotional component of the disease [67]. Indeed, we know that the afferences of this nerve, which terminate in the nucleus of the solitary tract in the brainstem before projecting toward the amygdala and insula, transmit somatic information (Fig. 3.23, p. 163).

The Parietal Lobe

The parietal lobe including areas 3, 1, and 2, which receive somatosensory inputs (touch, position of the muscles and joints, temperature), is located behind the

[54] Cf. Vagus nerve stimulation in depression treatment p. 241.

central sulcus. The upper portion of this lobe is also considered a heteromodal associative cortex and plays an important role in the integration of visual, tactile, and auditory (areas 5 and 7) information. This region is involved in spatial perception and motor coordination, also called praxis, but its role in managing emotions remains modest.

The Occipital Lobe

Located in the most posterior part of the brain, the occipital lobe contains the sensory areas for vision. Area 17 is the primary reception center, area 18 is devoted to perception, and area 19, the most peripheral, is devoted to interpretation. This lobe is not directly involved in emotions.

The Hypothalamic-Pituitary Axis and the Septal Area

Abstract The hypothalamus can be seen as an emotional transducer that converts the information received from the amygdala, the insula, the orbitofrontal cortex, and the rest of the limbic system into autonomic (quickening or slowing of heart rate, respiratory changes, digestive changes…) and endocrine responses. The pituitary gland, under the control of the hypothalamus, is involved in the endocrine response including the secretion of corticotropic hormones during stress phenomena.

The hypothalamic-pituitary axis and the neighboring septal area, both belong to the limbic system. The hypothalamic-pituitary axis is an essential region participating in a great number of functions. In particular, it helps maintain the balance—homeostasis of our internal environment by regulating thirst, hunger, body temperature, and sleep, thus ensuring our adaptation to the outside environment. The hypothalamus acts upon the organism through the *autonomic* nervous system, which is *independent* as well as via hormones. It is the pituitary gland, gland under the control of the hypothalamus, which is responsible for this humoral mediation.

The Hypothalamus

The hypothalamus is located at the base of the brain toward the front underneath the thalamus, from which it takes its name. This small 4 cm^3 structure weighing about the same number of grams is involved in many functions. The hypothalamus lines the anterior walls of the third ventricle and contains a dozen nuclei. For the sake of anatomical and functional clarity, we will describe this region from the center to the periphery and from front to back (Fig. 2.11).

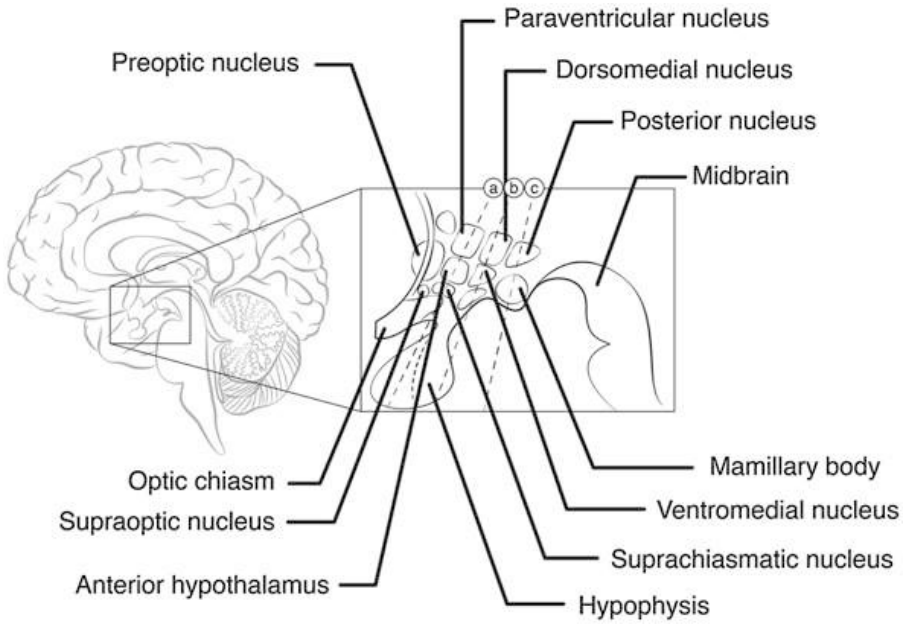

Fig. 2.11 The hypothalamus. General view

From the center outwards, three zones can be distinguished: periventricular, medial, and lateral (Figs. 2.12, 2.13, and 2.14). The periventricular zone, bordering the ventricular walls, regulates hormonal secretion of the anterior pituitary. The medial zone includes the supraoptic and paraventricular nuclei, which both secrete antidiuretic hormones (ADH) and oxytocin, two peptide hormones which are sent to the posterior pituitary to be released (Fig. 2.16, p. 73). The paraventricular nucleus, heavily involved in controlling stress responses, contributes to the secretion of *corticotropin-releasing hormone* (CRH) and regulation of the sympathetic system. This nucleus receives information from the amygdala, hippocampus, prefrontal cortex, and the locus coeruleus.[55] The paraventricular nucleus is therefore an essential relay in the integration of neuroendocrine and autonomic responses to stress. Secretion of CRH, as well as DHA, stimulates synthesis of adrenocorticotropic hormone (ACTH). Stimulation of these neurons during stress causes the release of ACTH, which causes the release of glucocorticoids from the adrenal glands. Glucocorticoids increase the rate at which carbohydrates and proteins are metabolized (Fig. 2.15, p. 73). These various physiological reactions in response to stress are intended to induce the famous "fight or flight" behavior meant to help the organism deal with the stressful stimuli. This can result in aggressive behavior, fear, or even passivity, and may inhibit appetite and reproductive behavior, through disruption of the menstrual cycle and libido. The medial

[55] Activation of the locus coeruleus induces the release of norepinephrine in the brain, provoking an increase in attention, memory performances but also anxiety. The "facilitator" effect that norepinephrine has on the hippocampus encourages the remembering of a menacing event's context.

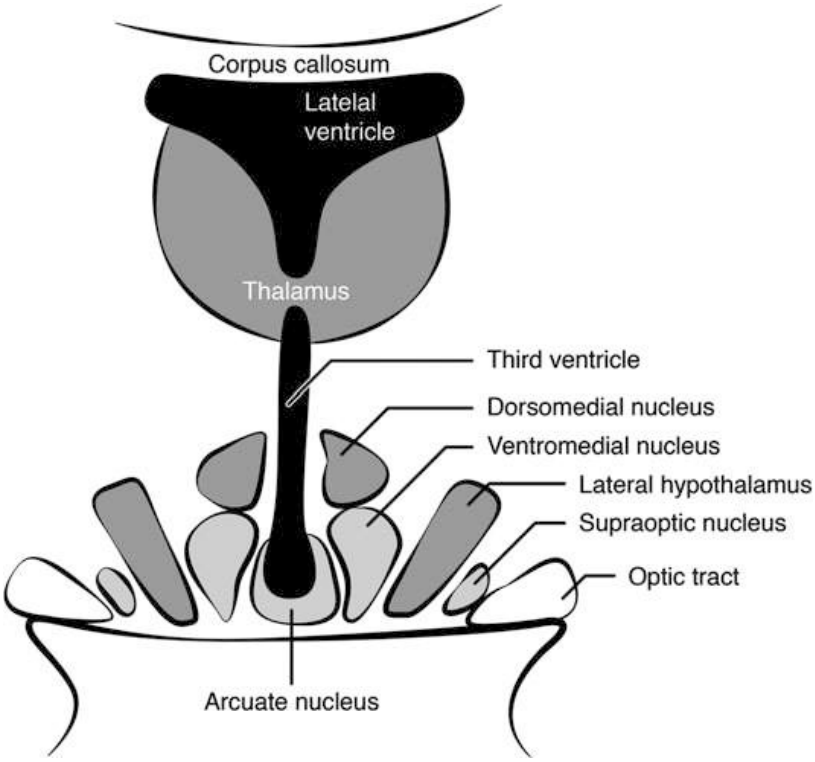

Fig. 2.12 Medial hypothalamus (Section B)

zone is also the location of the dorsomedial and ventromedial nuclei both of which are responsible for behaviors relating to hunger and thirst as the ventromedial nuclei[56] are implicated in sensations of satiety. Surgical lesioning of this structure leads to increased appetite followed by obesity. The opposite occurs following electrical activation of the core: reduction in food intake and body weight and activation of lipolysis [68]. Finally, the lateral zone, under the control of the cortex and amygdala, is also involved in feeding behavior, but its action is opposed to that of the ventromedial nucleus since it promotes consumption. Following lesions in the lateral zone, weight loss [69] and even cachexia have been observed [70–72]. In contrast, electrical stimulation of these areas increases food intake, body weight, and lipogenesis [73]. In 1974, the Dane Quaade, was the first to propose thermal lesioning of the lateral hypothalamus for the treatment of patients with morbid obesity.[57] A *lateral hypothalamotomy* was performed in five patients weighing between 118 and 180 kg. The Copenhagen-based endocrinologist reported a decrease in transit, appetite, and weight in these patients [74]. Some authors believe that the weight gain often observed in patients undergoing stimulation of the subthalamic nucleus may be due to the proximity of this structure to the lateral

[56] In the ventromedial nucleus this is controlled by a hormone secreted by the leptin, the white adipose tissue (from the greek λεπτός, leptos, "thin") sometimes called the "hunger hormone."

[57] Cf. p. 374.

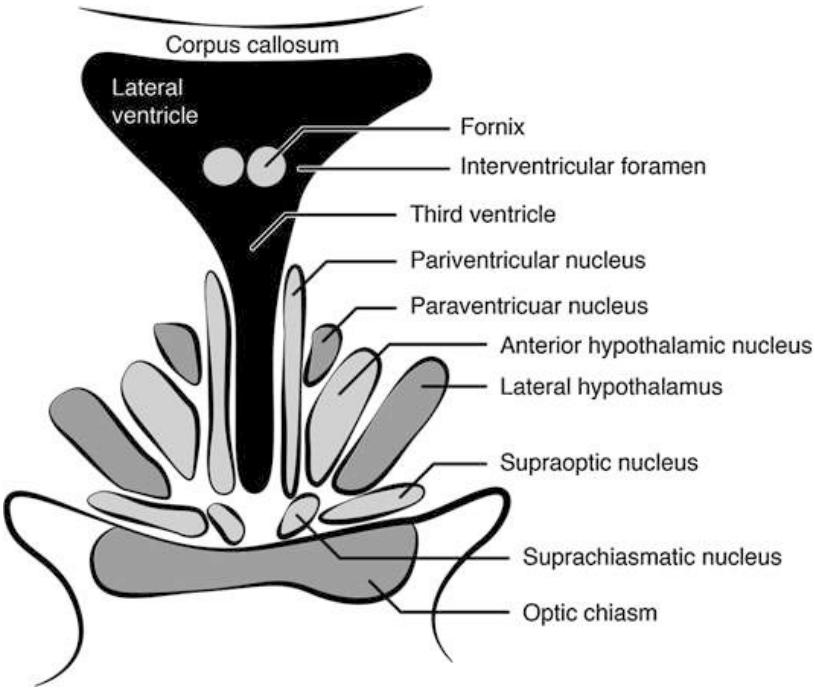

Fig. 2.13 Anterior hypothalamus (Section A)

hypothalamus [75–77]. Current research protocols[58] seek to evaluate the effectiveness of neuromodulation by electrode of the lateral hypothalamus in patients with morbid obesity (IMC > 40 kg/m^2) linked to hyperphagia [78].

To this center-outward segmentation is added a front to back subdivision. The anterior region (Fig. 2.13), located above the optic chiasma, comprises the suprachiasmatic nucleus which along with the pineal gland, helps synchronize the circadian clock to the light–dark cycle. The preoptic nucleus which is involved in thermal regulation and endocrine regulation of sexual behavior. Electrical stimulation of the preoptic nucleus reproduces all the signs of parasympathetic activity.[59]

The posterior region includes the aptly named posterior hypothalamus along with the mammillary bodies which are involved in memorization via the Papez circuit[60] (Fig. 2.14). Given that aggressive behavior results, among other things, in sympathetic manifestations, the neurosurgeon K. Sano proposed in the 1970s to treat patients suffering from hyper-aggressiveness with lesions of the posterior hypothalamus[61] (Fig. 2.15).

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[58] Cf. p. 375.

[59] Its activation leads to a general slowing of the organism's functions to preserve energy. All that was augmented, dilated, or accelerated by the sympathetic system is now decreased, contracted, and slowed. Only the digestive function and the sexual appetite are favored by the parasympathetic system. The latter is associated with a neurotransmitter, acetylcholine.

[60] Cf. Papez circuit (Fig. 2.24, p. 85).

[61] Cf. section on aggressive behavior disorders p. 352.

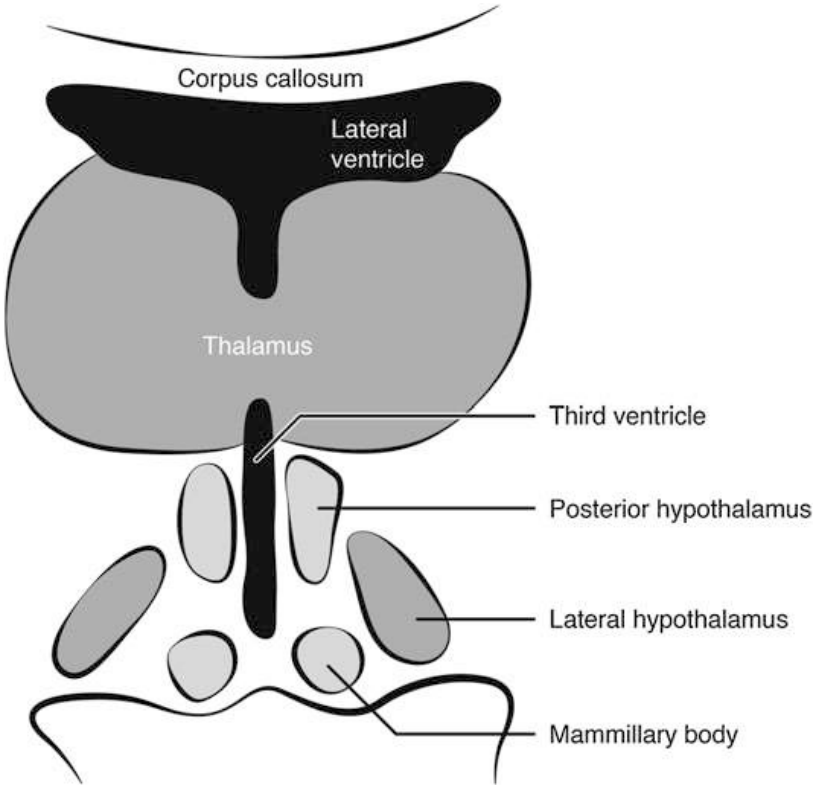

Fig. 2.14 The posterior hypothalamus (Section C)

At first, the Tokyo-based surgeon conducted electrical stimulation of the hypothalamus in patients who, for the most part, had brain damage and mental retardation. After demarcating this *ergotropic*[62] region, a lesion was made bilaterally using thermocoagulation. This *posterior hypothalamotomy*, procedure which he performed on 51 patients led to improvement in 95 % of patients after at least 2 years [79, 80]. Weight gain was probably due to the procedure's impact on the neighboring ventromedial nuclei. More recently, a Paris team led by Agid observed unexpected outbursts of aggression during deep brain stimulation of a patient with Parkinson's [81]. Imaging revealed that the electrodes were not located exactly at the level of the subthalamic nuclei, as the procedure calls for, but in the posterior part of the hypothalamus. In Milan, Franzini and Broggi, have since 2000 been successfully targeting this region for the treatment of patients presenting severe aggressive behavior stemming from brain damage (perinatal toxoplasmosis, head injury, cerebral anoxia…) [51]. This structure has also been targeted for the treatment of *cluster headaches*, excruciatingly severe headaches. Functional imaging studies have revealed that in such patients this region, especially its lower portion, is

[62] An "ergotropic" region is a zone controlled by the sympathetic system. Here describing a triangular area of the hypothalamus centered around the "CA-CP" axis connecting the anterior and posterior commissures (Fig. 3.2, p. 109), the top of Sylvius aqueduct and the anterior area of the mammillary bodies (Fig. 2.11, p. 68), this region is also known as "the triangle of Sano."

hyperactive [82]. Curiously though, this hyperactivity is not associated with increased aggressive behavior. Brain stimulation of the posterior hypothalamus is currently being evaluated for use in the treatment of untreatable cluster headaches, which can be so intense as to drive affected people to suicide [51, 83]. The posterior region of the hypothalamus, as we have seen, also contains an extension of the mammillary bodies, the fornix. Research protocols are underway to assess whether stimulation of these bundles improve memory performance. Research began following an unexpected clinical response during a session of deep brain stimulation. In 2008, Lozano and his team in Toronto stimulated the ventromedial nucleus of the hypothalamus of a conscious patient with morbid obesity. The purpose of the procedure was to determine if the patient felt decreased appetite during high-frequency stimulation of one or more of the different parts of the ventromedial nucleus. Instead of the sought-after response, during the procedure the patient keenly recalled a scene in a park with his friends which had occurred 30 years prior. Neuropsychological tests showed significant improvement in biographical memory after each stimulation [61]. Imaging showed that the electrodes were in fact located closer to the fornix than to the ventromedial nuclei. This serendipitous discovery led the Canadian team to explore the approach in the treatment of Alzheimer's patients. Clinical studies[63] have been initiated in the hope that stimulation of the fornix can halt memory loss associated with this disease [62].

The Pituitary Gland

Protruding off the bottom of the hypothalamus, the pituitary gland rests in a small bone cavity and consists of an anterior and posterior portion: the anterior pituitary (also called adenohypophysis) and posterior pituitary. The adenohypophysis is regulated by neurons in the hypothalamus and secretes releasing factors which act on the glands of the body. Thus, luteinizing hormone(LH) and follicle-stimulating hormone (FSH) stimulate release of sex hormones (progesterone, testosterone). Thyrotropin-releasing hormone stimulates the thyroid gland while prolactin contributes alongside oxytocin to lactation. The adrenocorticotropic hormone[64] is a releasing factor for hormones secreted by the adrenal gland. Produced especially during stressful situations, is a releasing factor for hormones secreted by the adrenal gland. Produced especially during stressful situations, prepares the individual to respond to environmental stresses (Fig. 2.15). However, sustained release can have deleterious effects on the hippocampus by causing atrophy and impairing declarative memory[65] as, for example, in cases of sustained stress [77] or Cushing's syndrome, characterized by abnormally high levels of cortisol in the blood [85, 86].

Two hormones synthesized in the hypothalamus are discharged in the posterior pituitary (Fig. 2.16): the antidiuretic hormone, which prevents leakage of water

[63] See, p. 200, phenomena of plasticity and neurogenesis related to stimulation.

[64] Cf. p. 113.

[65] Cf. definition p. 135.

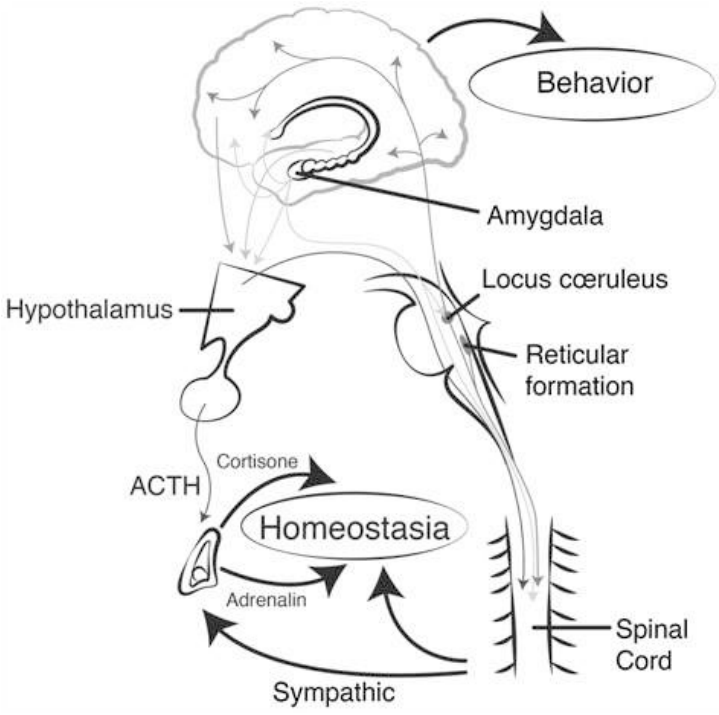

Fig. 2.15 Hypothalamus and stress. Adaptation to stress results in an increase in cardio-respiratory rate, increased blood pressure, analgesia, mobilization of energy—via glucocorticoids—through increased glucose uptake in muscles. Inhibition of anabolic pathways with slower digestion and growth and decreased immunity and reproduction is also observed

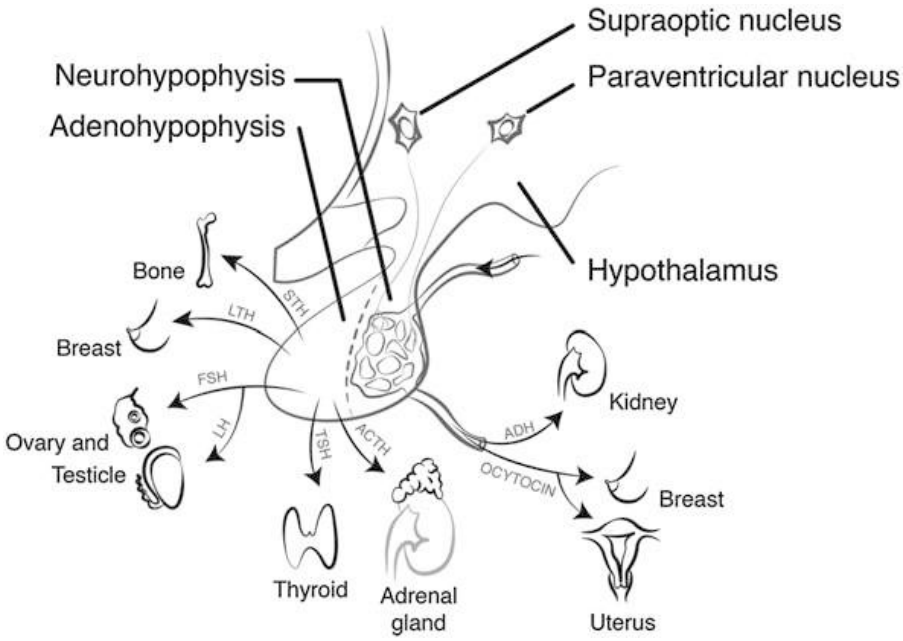

Fig. 2.16 Pituitary gland and hormonal secretions

from the kidney, and oxytocin. This hormone which participates in lactation may also be involved in shaping the mother–child bond, social phenomena, some instances of solidarity, altruism, and trust in others [87]. Intranasal administration of oxytocin could also improve the social behavior of patients with autism or Asperger syndrome [88]. Oxytocin nasal sprays may also be effective against the symptoms of schizophrenia when associated with an antipsychotic treatment [89].

The Septal Area

The septal area is located above the anterior commissure, in front of the thalamus, behind the beak of the corpus callosum, and below the *septum pellucidum*,[66] from which it derives its name. Its exact contour remains open to discussion. Some authors include neighboring lateral structures, such as the nucleus accumbens, or medial structures such as the subgenual cortex (area 25), or even the bed nucleus of the stria terminalis (BNST). The septal nuclei themselves can be divided into two groups: a medial group and a lateral group. Medial nuclei have reciprocal connections to the hippocampus—via the fornix—and receive information from the lateral nuclei. The septal nuclei are reciprocally connected to the lateral hypothalamus and receive information from the cingulate cortex. They have projections to the lateral habenula headed for the ventral tegmental area (VTA)—via the median forebrain bundle (MFB) (Fig. 2.30, p. 93) and the periaqueductal gray matter. This last region is responsible for feelings of well-being or analgesia[67] through the release of endorphins, natural opioids, while the lateral habenula influences the release of dopamine, serotonin and norepinephrine.[68] If we include within the septal area the BNST, the many connections mentioned above, and connections rooted in the amygdala, we see that this region is a strategic node in the modulation of emotions, particularly those associated with positive reinforcement. This region therefore quickly became the focus of research into deep brain stimulation. In 1954, Olds and Milner of McGill University in Montreal, conducted electrical stimulation of this area in rats [90]. The neurophysiologists observed that it caused the animal subject intense pleasure. Such pleasure, in fact, that given the opportunity to stimulate itself, the animal would neglect all other activities to the point of jeopardizing its survival. At the same time, the American Heath announced that a schizophrenic patient with intractable pain caused by a metastatic cancer was soothed by temporary electrical stimulation of this same region [91, 92]. Similar success was subsequently achieved in nonpsychotic patients with chronic pain [93] and since then, stimulation of the septal area has

[66] The septum pellucidum is a membrane separating the anterior horns from the lateral ventricles.

[67] The septal nuclei were also targeted for intractable pain treatment.

[68] The lateral habenula, which projects to all three neuromediator circuits, slowing them down, is one of the anatomical targets explored. It will be discussed (p. 226) in the section about chronic depression treatments using deep brain stimulation.

Table 2.1 Studies have described the effects of stimulation of the septal area in humans

Country, year	Number of patients	Clinical effect, (stimulation parameters)
United States, 1960 [98]	52	Feeling of well-being and wanting to continue the stimulation, (50 Hz, 1 ms)
The Netherlands [99]	6	More gay and more alert (1), (2–5 kHz, 0.02–0.06 ms, <12 V)
United States, 1972 [100]	1	Important sexual pleasure
Switzerland, 1985 [95]	10	Feeling of well-being (1 ms)

been offered to a very limited number of patients with intractable neuropathic pain [94] with encouraging results. Stimulation of the PAG could explain this efficacy [94, 95]. Heath and his team in New Orleans continued their "exploration" of this region, primarily in schizophrenic patients, and observed that sensations very similar to an orgasm could be elicited through stimulation [96]. The principal studies on stimulation of this area are summarized in Table 2.1 [97].

The Thalamus and the Basal Ganglia

Abstract The thalamus is a key center in the integration of sensory, motor, cognitive, and emotional information. Three of its nuclei—the anterior, medial dorsal, and ventral anterior nuclei—as well as a structure located at it base, the subthalamic nucleus, are implicated in emotions. The basal ganglia include an internal and external segment of the globus pallidus and the striatum, whose ventral region is involved in cognitive functions. Located at the base of the striatum, the nucleus accumbens is involved in the reward circuit. These different structures are integrated alongside the frontal cortex within circuits: the cortico-striato-thalamo-cortical loops that regulate our motor skill, cognition, and emotions.

The Thalamus

The thalamus (Greek: *θάλαμος thalamos,* inner chamber[69]) is a symmetrical structure located on each side of the brain forming the walls of the third ventricle (Fig. 2.17). Situated between the cortex and the brainstem, this set of nuclei relays and integrates motor, sensory, and sense information—with the exception of smell—and thus has many reciprocal connections to the cortex. We will limit our discussion to the structures involved in emotional: the anterior, ventral anterior, and medial dorsal nuclei.

[69] According to the first anatomists, the visual pathways seemed spread over this "bed," the "thalamus nervorum opticorum."

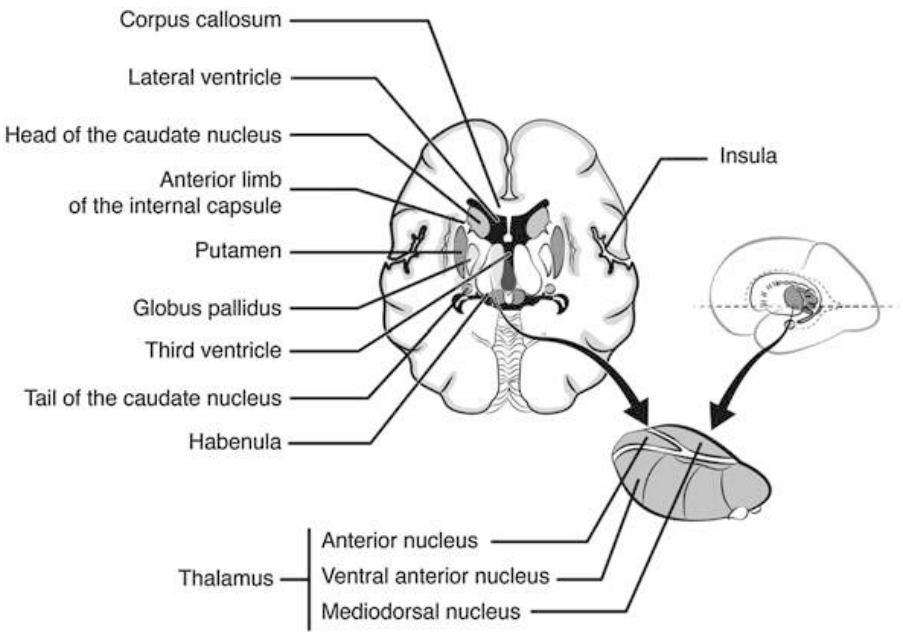

Fig. 2.17 The thalamus

The Anterior Nucleus

The anterior nucleus receives information from the hippocampus via the mammillary bodies[70] which, once integrated, is sent to the cingulate cortex. It is part of the Papez circuit involved in memory[71] (Fig. 2.24, p. 85). This nucleus is currently being targeted in DBS research into the treatment of intractable forms of epilepsy [101–103].

The Ventral Anterior Nucleus

Afferents of the ventral anterior nucleus emanate mainly from the internal globus pallidus (GPi), while its efferent fibers project toward the dorsolateral and orbitofrontal cortex. This nucleus is involved in an associative cortico-striato-thalamo-cortical (CSCT) loop devoted to cognitive processes (Fig. 2.27, p. 89) [109].

[70] Two nuclei of the hypothalamus cf. p. 118.

[71] Cf. the anatomical description of this circuit p. 133.

The Dorsomedial Nucleus

The dorsal medial nucleus receives inputs from the hypothalamus, amygdala, olfactory cortex internal globus pallidus, and the neighboring thalamic nuclei. Once integrated, the information is projected onto the entire prefrontal cortex, and, in particular, the anterior cingulate cortex. This nucleus participates in the CSTC loop (also called "limbic" loop) involved in emotions (Fig. 2.28, p. 91) [104].

The Associative Thalamocortical Connections

These three thalamic nuclei are reciprocally connected to the prefrontal cortex by several thalamocortical tracts that run between the caudate nucleus and the putamen. This band of white matter forms the anterior part of the internal capsule and constitutes its anterior limb. The posterior limb of the internal capsule is composed of a bundle of axons—the pyramidal tract—which originates in the motor center and controls movement on the opposite half of the body (Fig. 2.18).

Within the anterior limb of the internal capsule (ALIC), two thalamocortical tracts are of interest to us: the so-called *associative* tract connecting the orbitofrontal and dorsolateral cortices to the ventral anterior and medial dorsal nuclei of the thalamus, and the *limbic* tract connecting the orbitofrontal and cingulate cortices to the dorsal medial nucleus [105]. These two bundles interest us because they are the targets of two psychosurgical procedures of the ALIC: the anterior capsulotomy[72] which creates lesions in these bundles (Fig. 3.6, p. 114). DBS, which blocks their operation through the application of an electrical current (Fig. 2.19).

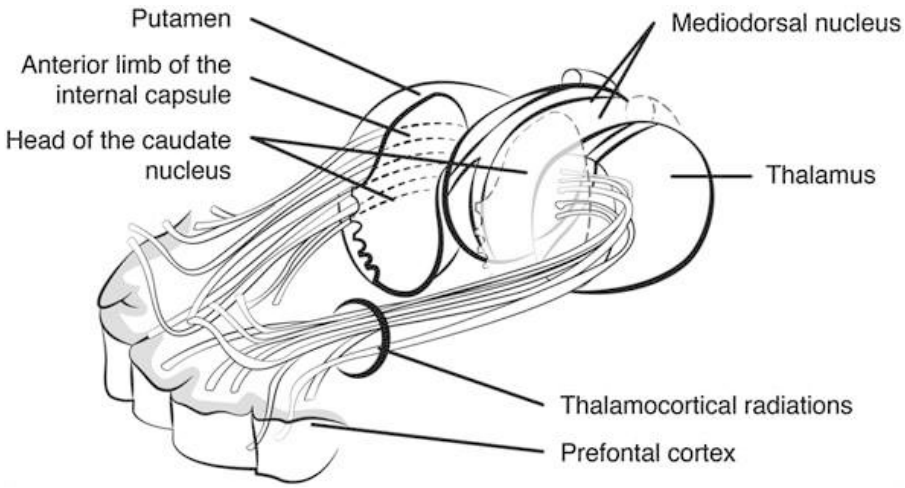

Fig. 2.18 Thalamocortical radiations projecting through the anterior limb of the internal capsule to the prefrontal cortex. According to [112]

[72] Cf. the historical p. 51, the thermocoagulation p. 167 or radiosurgery surgical technique p. 188, its results in obsessive–compulsive disorder p. 284 or in depression p. 326.

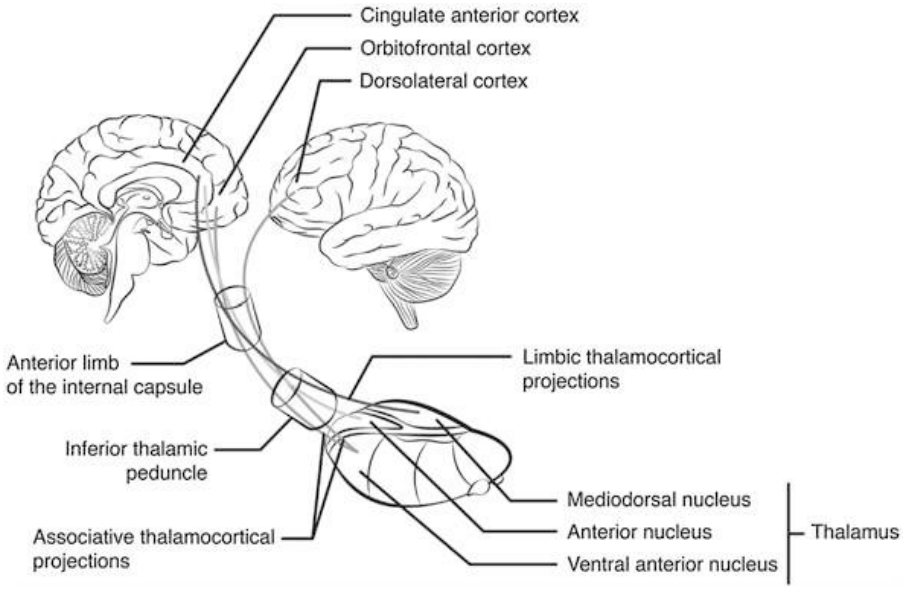

Fig. 2.19 Thalamocortical associative and limbic connections

The Subthalamic Nucleus

This paired nucleus (found on each side of the brain) in the shape of elongated lens of about 150 mm^3 is situated, as its name suggests, on the ventral side of the thalamus. It was discovered by the French neurologist JB. Luys and used to be known as the *corpus Luys* (Fig. 2.20).

The subthalamic nucleus (STN) contains glutamatergic excitatory neurons receiving afferences from the prefrontal cortex, substantia nigra and external globus pallidus. It projects, in turn, primarily onto the internal globus pallidus and thalamus. Involved in various CSTC loops,[73] the STN modulates motor, cognitive, and emotional responses. These three functions correspond to three anatomical areas. The area tasked with emotions, called the limbic area, is situated toward the rear. The cognitive areas occupies the lateral portion of the nucleus [106]. The motor area is the main target for deep brain stimulation used in the treatment of Parkinson's disease and is being evaluated for the treatment of OCD, as discussed in later section.[74] Uncertainty remains as to the exact emotional and cognitive functions of this structure. Nonetheless, some of the undesirable side effects of high frequency electrical stimulation, which is considered to inhibit this structure, may shed some light on the possible role of this nucleus. At the cognitive level,

[73] Cf. p. 139.

[74] Cf. p. 292.

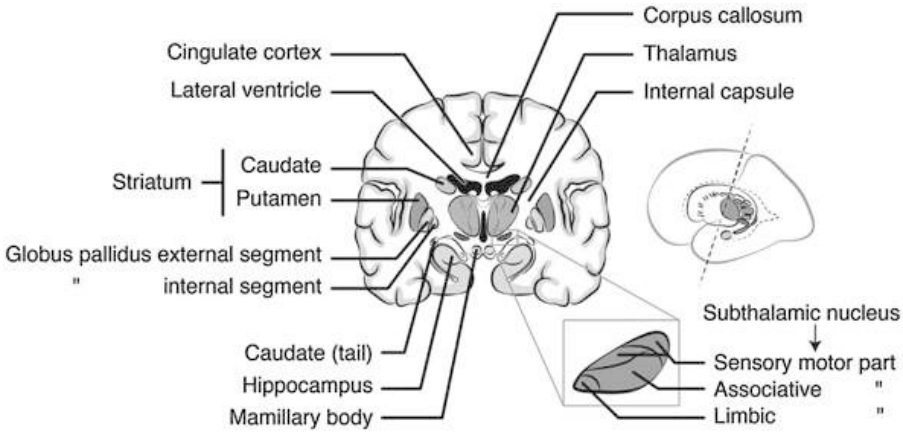

Fig. 2.20 The subthalamic nucleus

DBS of the nucleus can result in decreased verbal memory and fluency [107–116], executive functions [111, 112, 117–120], and attention [121, 122]. In terms of its effects on mood, symptoms can range from mania [115, 123–125], depression [111, 114, 125–139] or even suicide [119, 132, 140] as well as personality disorders [107, 133], increased anxiety [111, 113] and hypersexuality [119, 125, 141–145]. These diverse and sometimes contradictory effects are evidence, on the one hand, of the complexity of the STN, and on the other, of the still poorly understood mechanisms of high frequency stimulation. One may also wonder whether the clinical effects obtained are brought on by the combination of the activation of the fibers surrounding the nucleus and the inactivation of the neurons it contains. The exact position of the electrode within the structure and the electrical parameters also plays a key role.[75]

The Striatum and the Pallidum

The striatum is a striated (hence, its name) paired nerve structure composed of two interconnected dopaminergic entities of identical embryological origin: the caudate nucleus and the putamen. The caudate nucleus, shaped like a horseshoe, wraps around the thalamus (Figs. 2.21, 2.22).

It has a bulbous frontend and elongated body tapering off just behind the amygdala. The head of the nucleus is connected to the putamen by "putaminocaudate," bridges crossing the internal capsule, including the ALIC. The putamen resembles a pyramid and its interior portion faces the pallidum. The pallidum, also

[75] Cf. Mysteries of DBS p. 198.

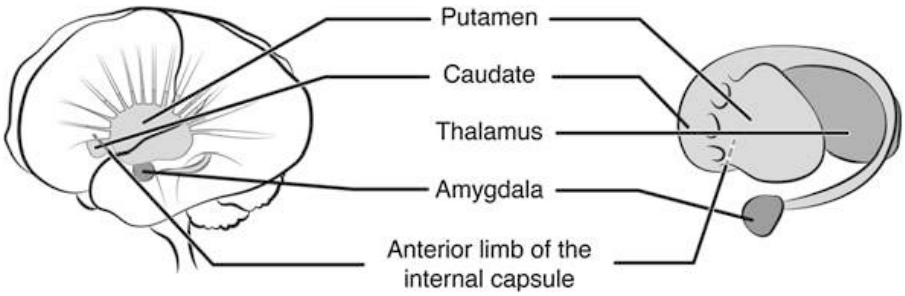

Fig. 2.21 The basal ganglia

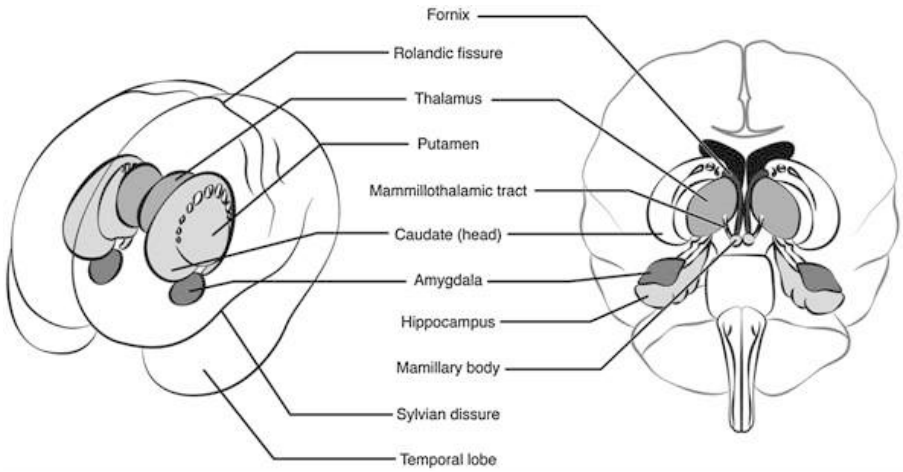

Fig. 2.22 Side and anterior view of the basal ganglia

called globus pallidus, consists of two segments, the external globus pallidus (GPe) and the internal globus pallidus. The motor sector of the GPi includes the lateral, ventral, and posterior portions. The limbic sector follows the anterior ventral–medial axis, and the remaining area is the associative sector. The putamen and pallidum form an anatomic entity: the lenticular nucleus.

The striatum is divided into an upper, dorsal part, and a lower, ventral part. The dorsal striatum is involved in motor control and cognition. Its role appears crucial to routine habits [146, 147]. The ventral striatum, however, takes part in the regulation of emotions and behaviors, especially the initiation and execution of behaviors involving the notion of reward [21]. In front and at the base of the ventral striatum where the putamen and the head of the caudate nucleus meet is located a critical structure, the nucleus accumbens (Fig. 3.3, p. 110).

The striatum is divided into an upper, dorsal part, and a lower, ventral part. The dorsal striatum is involved in motor control and cognition. Its role appears crucial to routine habits [154, 155]. The ventral striatum, however, takes part in the regulation of emotions and behaviors, especially the initiation and execution of

behaviors involving the notion of reward [21]. At the bottom and in front of this ventral striatum there is a key structure: the nucleus accumbens, which corresponds to the fusion between the putamen and the caudate nucleus.

The Nucleus Accumbens

Abstract Situated at the base of the ventral striatum, the nucleus accumbens consists of a "core," involved in motor control, and a "shell" connected to the amygdala and the rest of the limbic system. Functioning as a relay within the CSTC loop, this nucleus helps regulate emotions and motivation, and as such, it is considered the interface between desire and action.

Because of its importance in psychosurgery, the nucleus accumbens, situated at the base of the ventral striatum merits particular attention. It is the interface between two fundamental circuits in the regulation of emotions and behavior: the CSTC loops and the reward circuit.[76] For histological reasons, the nucleus accumbens is composed of a "core," and a "shell" [112].

The shell is where the ends of the mesolimbic dopamine[77] releasing neurons come together. Dopamine, the crucial fuel of the reward circuit, is inseparable from the motivational processes of the limbic system. The core of the nucleus is connected to the extrapyramidal motor system responsible for regulating movement via the CSTC motor loop. This core can be likened to a strategic gate between the limbic and extrapyramidal systems, an "interface between motivation and action" [148]. It is possible that overactivity in one of these CSTC loops causes OCD. French and German teams have therefore suggested modulating this system through implantation of stimulation electrodes in the nucleus accumbens[78] [149–151]. The nucleus accumbens also receives excitatory afferents[79] (Fig. 2.23) from the amygdala [152], hippocampus [152–155], thalamus [156, 157] and orbitofrontal cortex [158]. It is believed that the nucleus accumbens integrates environmental information via the hippocampus, information on the emotional context via the amygdala and cognitive data through its connections to the prefrontal cortex. It draws on this information to contribute to the selection of an appropriate behavioral response to a given situation. Its function would appear crucial in motivational behavior—sex, addiction, or stress related. As such, it seems to play an important role in adapting behavior and the learning process [159]. The accumbens nucleus in turn, projects to the ventral pallidum through

[76] Cf. p. 146.

[77] Ibid.

[78] Cf. p.291.

[79] These excitative afferents are mediated by glutamate, a neurotransmitter that stimulates the central nervous system (CNS).

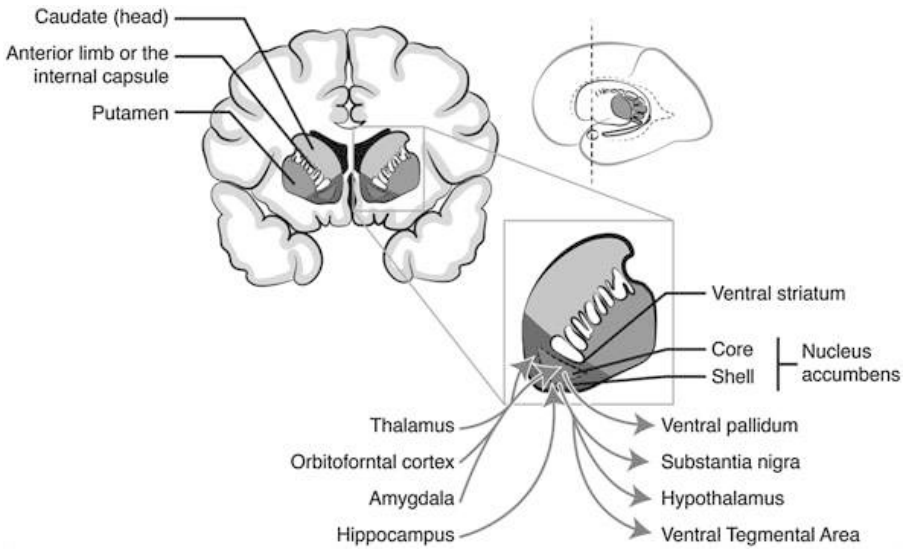

Fig. 2.23 The nucleus accumbens and its connections

inhibitory efferents[80] [160–162] and to the ventral segmental area (VTA) and substantia nigra. The latter two structures are the primary dopamine producing areas [163, 164]. The shell also has efferents to the lateral portion of the hypothalamus [165]. In 1954, a study showed that rats with a stimulating electrode, which they were able to activate themselves, implanted in the VTA resorted to endless sessions of autostimulation, even to the point of compromising their food-intake and starving themselves to death [90]. Similar effects were subsequently obtained when the electrodes were implanted in the nucleus accumbens [166]. The animal subject would stimulate itself up to 20 times a minute [167–169]. The administration of morphine [170, 171], however, reduced the amount of autostimulation. It was later shown that all drugs increase the concentration of neurotransmitter in the shell of the nucleus accumbens [172, 173] which explains why an influx of dopamine decreased the frequency of autostimulation. Similarly, when weaning off an addictive substance, there is a steep reduction in the release of dopamine in the shell [174]. When a male rat is placed in the presence of a female rat in heat the level of dopamine in the shell increases, and if he is able to engage in the reproductive act, it skyrockets. In humans, functional imaging shows activity of the nucleus accumbens when pleasant or erotic scenes are being viewed [175, 176]. This has led some authors to call this nucleus the "pleasure center." This hedonistic[81] attribute has encouraged teams to successfully target this nucleus

[80] These inhibitory afferents are mediated by GABA (gamma-aminobutyric acid) a neurotransmitter that inhibits the CNS.

[81] Hedonism comes from the Greek word *ηδονή*, which means pleasure. It is a doctrine that has as moral principle the search for pleasure and the avoidance of pain.

with deep brain stimulation in order to treat intractable depression[82] [177, 178]. Given that one of the major symptoms of depression is anhedonia,

German researchers have suggested that neuromodulation by stimulation of the nucleus could likely reduce the symptoms resulting from loss of pleasure [179]. From 1970 to 1976, another German team performing subcaudate tractotomies[83] on patients with severe OCD noticed during follow-up that 8 of the 16 patients had developed a severe addiction. In 1998, MRI scans showed that the lesions were in fact located in the ventral striatum and that in six of the patients they were located in the nucleus accumbens [180]. Based on these findings, animal testing and functional imaging data, this nucleus is currently being studied as a target for treatment of certain addictions using deep brain stimulation[84] (Table 4.13, p. 246) [181–185]. It should be noted procedures involving ablation of the nucleus accumbens, though ethically questionable, are also offered to patients addicted to opiates [186].

Emotion and Its Circuits

Abstract Several tightly interconnected neural circuits are involved in emotions. The Papez circuit, which includes the hippocampus, thalamus, and mammillary bodies, is involved in memory. Two other loops connecting the prefrontal cortex to the striatum and thalamus and returning to the cortex also carry cognitive and emotional information. This last loop, the emotional loop, is connected through the nucleus accumbens with the dopamine pathway involved in reward-based motivational processes. Other more diffuse circuits of neurotransmitters—serotonin and norepinephrine—are also involved in the regulation of mood.

A Brief History: The Papez Circuit

In 1937, James Papez theorized a possible circuit to account for emotion [5]. Based on research by Bard, who highlighted the role of the posterior hypothalamus in behavior characteristic of fury through experiments on decerebrated cats [187], Papez suggested that the hippocampus is also involved in emotion. It was known at the time that the hippocampus underwent histological changes in patients with rabies, known for their excessive emotional manifestations characterized notably by bouts of terror. In his original article, the neuroanatomist wrote that all

[82] Cf. p. 291.

[83] Subcaudate Tractotomy cf. p. 180.

[84] Cf. p. 193.

information from our senses is directed to the thalamus. There, the information is split into two streams: one for "thought" and the other for "feeling." The first stream heads for the sensory and cingulate cortices to transform sensation into conscious perception (sensory cortex) and thought (cingulate cortex). According to Papez, the cingulate cortex, depending on the emotional charge of the thought, then sends it toward the hippocampus and from there via the fornix, to the mammillary bodies of the hypothalamus. At this stage, the *emotional experience* is converted into a *physical expression*. The second stream heads directly to the mammillary body to convert some of the sensations into physical manifestations. This stream also influences the cingulate cortex which it reaches via the anterior nucleus of the thalamus. Drawing on the theory of Cannon-Bard[85] the American neuroanatomist hypothesized that emotional *experience* born in the cingulate cortex precedes emotional *expression* from the hypothalamus. Papez's theory, however, does not completely preclude James-Langes theory since information from the hypothalamus, i.e., emotional experience, also reaches the cingulate cortex. Ultimately, by describing this hippocampo-mammilla-thalamo-cortical circuit Papez primarily gave his name to a circuit involved in memory (Fig. 2.24). Clinical observation later confirmed the importance of the hippocampus in memory tasks. In 1954, the neurosurgeon W. Scoville performed a bilateral removal of the hippocampi in order to treat an epileptic patient who thereafter became unable to retain any information [188]. This case along with observations of animals showed that a bilateral lesion of one or more parts of the hippocampo-mammilla-thalamo-cortical circuit causes anterograde amnesia. All information from the cortex is funneled through the entorhinal cortex, the "gateway" to the hippocampus. From there, information reaches the mammillary bodies via the fornix and is then redirected to the anterior nucleus of the thalamus through the mamilla–thalamic tract.[86] The thalamus then projects to the cingulate cortex. In turn, the cingulate gyrus returns part of the data to the entorhinal cortex completing the circuit. The cortex is thus the primary input for information, and the Papez circuit projects back to the same cortex through successive iterations, which allow declarative memory[87] to be encoded. The connections between this circuit and the hypothalamus and amygdala explain the strong ties binding memory to emotion. Voltaire wrote, *that which touches the heart is engraved in the memory.* The reader

[85] Affective reaction—joy, disgust, enthusiasm, fear, anxiety and others—is a feeling qualified as "emotional experience," and according to Cannon and Bard it also provokes an "emotional expression" that manifests through neurovegetative signs, which become quantifiable. This causality is not unambiguous. As we know from experiments with certain relaxation techniques or meditation, it is possible to reduce the "emotional experience" by attenuating this "emotional expression." See the theory of James and Langes p. 84.

[86] Also known as the Vicq d'Azyr bundle, after the French physician that described it, Félix Vicq d'Azyr, Queen Marie-Antoinette's personal physician.

[87] Cf. its description p. 103.

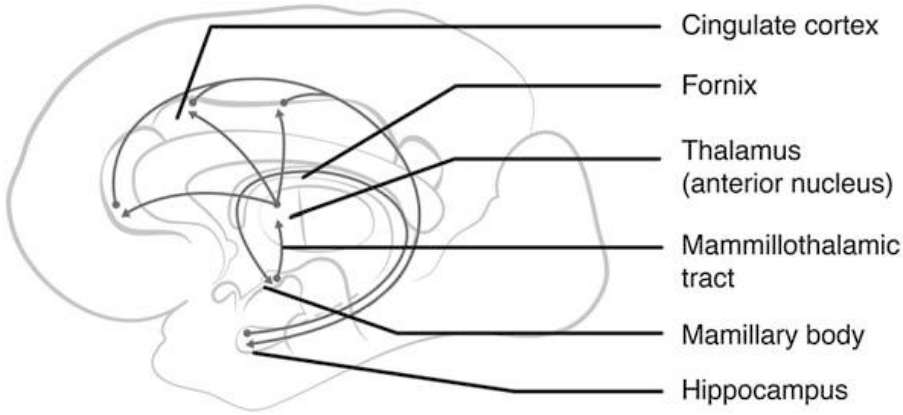

Fig. 2.24 Hippocampo-mammillary connections of the memory circuit

will recall precisely where she was on 11 September 2001 when the World Trade Center towers collapsed. The emotional nature of the event led to a "snapshot", which under normal circumstances would quickly be forgotten, being etched into memory [189, 190]. Thus stress resulting from certain events increases the release of norepinephrine and dopamine by the amygdala, which regulates the areas where these neurotransmitters are synthesized. Norepinephrine in turn activates the amygdala [51] with has specific receptors for this neurotransmitter. The amygdala then acts on the hippocampus, making it ready to place the event within the situational context and to assess whether the conditions for long-term memory creation are met or if the emotion-generating event can be forgotten [191]. Dopamine, meanwhile, appears to be more involved in long-term memory. VTA is the source of dopamine [192]. The signal causes increased release of dopamine. This influx of dopamine to the hippocampus improves the transmission of nerve impulses within the structure. Hence, efficacy and therefore memory is enhanced. Conversely, prolonged anxiety or stress negatively impacts declarative memory performance [193]. This memory impairment is related to the effect of glucocorticoids, hormones secreted during stress, on the hippocampus. Atrophy of the hippocampus can be observed after situations of long-term stress [84, 194] or because of excessive cortisol levels [85, 86]. In cases of extreme stress this can lead to complete loss of memory of the anxiety-causing event. In contrast, the amygdala, which is not affected by the action of these hormones, continues to set these events down in unconscious form as conditioned fear [195]. According to neuroscientist Marc Jeannerod, this phenomenon accounts for, "reactions such as phobias, war neurosis,[88] *panic attacks* [which] *may well find an explanation in this dissociation between amnesia of the circumstances surrounding the trauma and the persistent presence of conditioned fear* [196].

[88] Cf. Post-traumatic stress disorder p. 384.

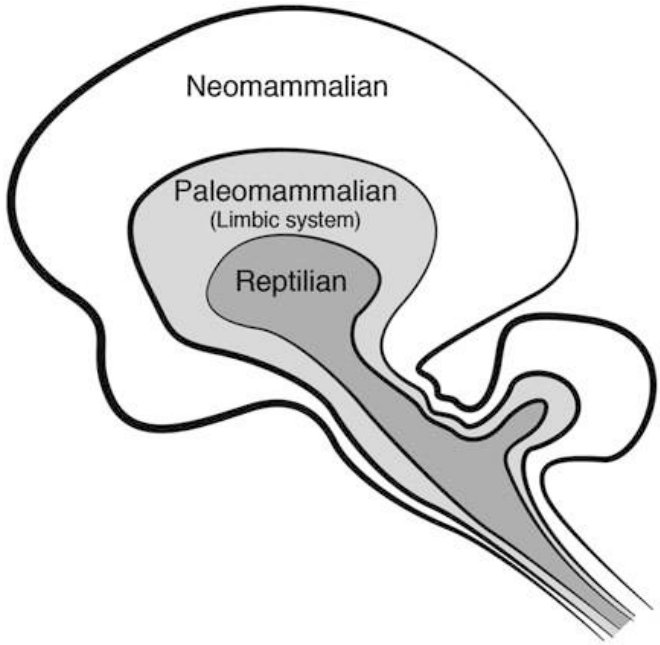

Fig. 2.25 MacLean triune brain, according to [206]

The MacLean Limbic System

In 1949, Paul MacLean offered a different mechanism for the neuroanatomy of emotions based not only on the Papez circuit but also on Darwinian evolution [197]. He saw the human brain as a stack of three brains (Fig. 2.25) [6].

According to MacLeans, this triune structure is the result of three concentric anatomical systems having been sequentially brought together in the course of evolution. A *reptilian brain*, composed of the basal ganglia and brainstem, controls functions such as arousal, eating, and reproduction. This primitive structure is overlaid by a *visceral* or *paleomammalian brain* later named the *limbic brain* [198]. Indeed, he considered that the great limbic lobe, described by Broca in 1878 [4], winds around the reptilian brain forming a limbic brain. In addition to the great limbic lobe of Broca[89] he also included the structures added by Papez, the thalamus and hypothalamus, as well as the prefrontal cortex and amygdala. The American scientist emphasized the close connections between the amygdala and the Papez circuit. The amygdala filters the information passing through the Papez circuit and is, as the psychiatrist Jouvent describes *the true watchman of the internal and external environment* […] *giving negative emotional valence, dangerous, or positive, favorable.* [The Amygdala] *receives information from converging sensory inputs (lateral nuclei). The sensory thalamus is its privileged partner* [199]. The connections between the amygdala (central nuclei) and the hypothalamus are

[89] The French neurologist associated this great limbic lobe with bestial behavior, opposing it to the intellectual faculties generated in the rest of the cortex.

responsible both for hormonal reactions, such as the release of glucocorticoid hormones, as well as autonomic responses which can involve the sympathetic or parasympathetic systems. Ultimately, MacLean attributed three functions to the limbic brain: self-preservation, inherent to the amygdalar region, the preservation of the species, i.e., sexuality, based in the septal region,, and finally inter-personal relationships, located within the thalamocingulate complex. According to the Yale researcher, this better evolved structure allows mammals to overcome stereotypical behaviors dictated by their reptilian brain by adding social skills, affective skills like emotions, and motivation. These two ancestral brains supposedly form *the horse*. The rest of the cortex, called neocortex, is the rider atop the horse. In other words, the neocortex represents rational intelligence which seeks to be free from emotions.[90] MacLean's anatomical model of emotion is often cited even though it has been much criticized. For example, it exaggerates the importance of the hippocampus, the mammillary bodies and the anterior thalamus, and underestimates the role of the basal ganglia in emotional processes [189].

The Cortico-Striato-Thalamo-Cortical Loops

MacLean's model leaves little room for the basal ganglia in the regulation of emotions. However, research by Alexander [104] has led to greater awareness of the fundamental role these nuclei have on how we function, especially emotionally. The model suggested by the Baltimore neurologist enables a clearer understanding of the involvement of the basal ganglia in our motor, cognitive, and emotional processes and their intricacies. Alexander has described a system composed of five parallel circuits involving the basal ganglia, the thalamus, and the frontal cortex. These five cortico-striato-thalamo-cortical loops (CSCT) connect the cortical areas to areas in the striatum and pallidum which in turn project back to the cortical areas via the thalamic nuclei. Of these loops, the best known is the one involved in sensorimotor functions. For this reason, it is interesting and informative to examine this loop in more detail. The limbic and cognitive loops of more direct relevance to the subject at hand, function very similarly.

The Motor Loop Circuit as an Example

This motor circuit (Fig. 2.26) involves the frontal motor cortex[91] (areas 4 and 6) and the parietal somatosensory cortex.[92] Both project to the dorsal striatum, or

[90] Read the excellent work by R. Jouvent (2009), Le cerveau magicien (The brain as magician) Odile Jacob, Paris.

[91] Cf. p. 90.

[92] Cf. p. 110.

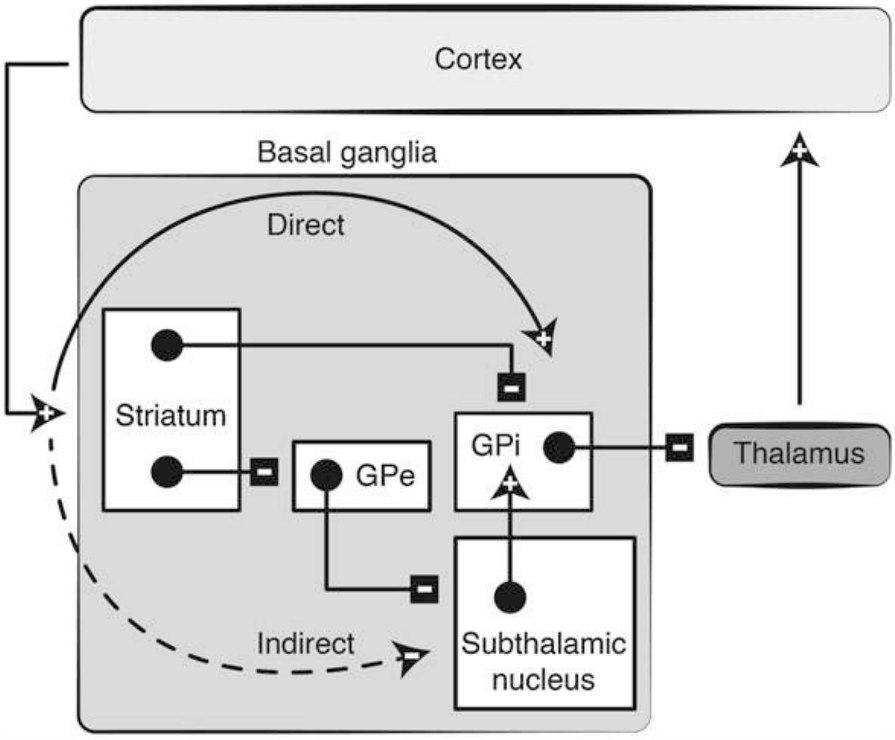

Fig. 2.26 The motor cortico-striato-thalamo-cortical loop (CSTC)

more precisely the putamen and have an excitatory effect through the action of glutamate, an excitatory neurotransmitter. The striatum then projects to the ventral part of the internal globus pallidus (GPi) and the substantia nigra (SN) slowing them both through the inhibitory action of GABA.

The GPi and SN then project to the motor nuclei of the thalamus, which they inhibit through the action of GABA. The thalamus in turn stimulates the cortex through the release of glutamate thus completing the loop. Within this circuit there are two separate pathways along which signals may travel. These two routes rely on different neurotransmitters in the striatum, solicit different structures, and have opposite effects. The first is the *direct route*, in which striatal neurons which synthesize GABA and substance P project an inhibitory input to the GPi and SN. The second is the *indirect route*, in which striatal neurons which synthesize GABA and enkephalin instead of substance P project an inhibitory input to the external globus pallidus (GPe). The GPe in turn projects an inhibitory input to the dorsolateral part of the subthalamic nucleus[93] (STN), which then projects onto the GPi and SN using glutamate. In the second scenario the GPi and SN receive an excitatory input. Activation of the direct route causes a decrease in the activity of the output nuclei (GPi and substantia nigra) leading to a disinhibition of the activity of the thalamus and thus release of glutamatergic excitatory impulses to

[93] Cf. anatomy p.126.

the cortex, which encourages movement. The direct pathway can be likened to the *accelerator pedal* in a car. In contrast, activation of the indirect pathway *brake pedal*. Which pathway is activated depends on the presence of dopamine, in the striatum: dopamine released by the substantia nigra activates the direct route and inhibits the indirect route. The associative and limbic circuits discussed below function according to the same model.

The Associative CSTC Loop

The associative circuit begins in the lateral and dorsolateral[94] orbitofrontal cortices and connects to the striatum near the head of the caudate nucleus and anteromedial portion of the putamen (Fig. 2.27) [8].

It then passes through the GPi and SN, before entering the thalamus through the inferior thalamic peduncle and reaching the ventral anterior[95] and nuclei, which link back to the prefrontal cortex [200]. This pathway corresponds to the *direct route* mentioned above. In the *indirect pathway*, the GPe and ventromedial portion of the STN are interposed between the striatum and the GPi. In terms of cognition, the associative loop seems to be implicated in working memory, spatial orientation, as well as executive functions relating to attention and preparation or initiation of actions. This circuit also intervenes at the emotional level by enabling empathy and appropriate responses during social interactions [200]. Decreased levels of dopamine within this circuit may cause the cognitive slowing and apathy observed in patients with Parkinson's disease [201]. In contrast, increased dopamine levels causes cognitive impulsiveness, tachypsychia, and novelty seeking.

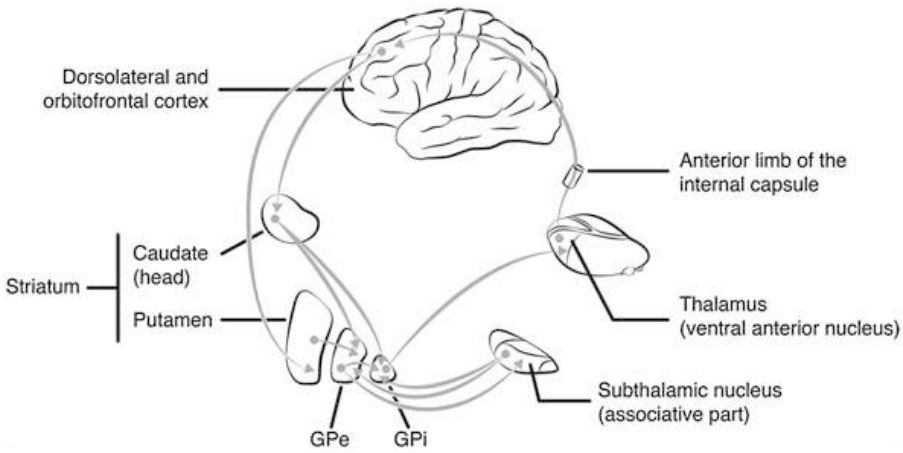

Fig. 2.27 The associative cortico-striato-thalamo-cortical (CSTC) loop. According to [209]

[94] Cf. p. 93.

[95] Cf. p. 124.

Psychomotor retardation (Fig. 4.4, p. 216) observed in cases of severe depression is probably related to dysfunction of this circuit [202, 203]. The struggle to push away negative thoughts or to ignore pain could also be related [202–206]. A targeted lesion within these structures, particularly in the orbitofrontal cortex, is likely to lead to personality changes such as impulsiveness, emotional lability, or a lack of "tact" when dealing with others [207, 208]. When instead the lesion is located in the dorsolateral cortex, the patient may exhibit perseveration, impaired planning for and adaption to new tasks, or difficulty blocking out external stimuli [207, 208].

The Limbic CSTC Loop

The limbic circuit begins in the anterior portion of the cingulum[96] (areas 24) and orbitofrontal cortex [8] and projects to the limbic (i.e., ventral) area of the striatum. This area comprises the ventral regions of the caudate nucleus and putamen and the nucleus accumbens (Fig. 2.28).[97]

The ventral striatum also has afferent connections from the amygdala[98], the hippocampus[99], and the entorhinal cortex.[100] Its efferent connections project onto the ventral globus pallidus which acts as a relay within the dorsomedial nucleus of the thalamus.[101] The limbic circuit also contains an *indirect pathway* in which the GPe and the rostral part of the STN intervene between the ventral striatum and the GPi. This loop circuit is involved in motivational aspects of behavior. In Parkinson's patients, low levels of dopamine in the limbic loop—as in the associative loop—causes cognitive slowing and apathy [201]. Extensive bilateral lesioning of the cingulate cortex[102] can lead to varying degrees of diminished motivation including apathy, aboulia, and mutism. In certain instances, verbal expression is limited to monosyllabic responses and the face no longer conveys any emotion, even in response to pain [207–209]. In fact, pain is no longer perceived as suffering. The different loops presented here almost always act in concert and share the same structures and neurotransmitters [200]. Their interrelatedness can be illustrated as follows: if you fancy a lemonade, this implies motivation (limbic loop); planning to reach the bottle (cognitive loop); and motor behavior to pour the lemonade into a glass and drink (motor loop). The STN, which is involved in all three loops, seems to play a key role in interfacing cognitive manifestations,

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[96] Cf. p. 95.

[97] Cf. p. 129.

[98] Cf. p. 98.

[99] Cf. p. 103.

[100] The entorhinal cortex (areas 28 and 34) is located in the internal part of the temporal lobe, it is an area of convergence for information proceeding from the associative cortex to the hippocampus.

[101] Cf. p. 123.

[102] Cf. p. 95.

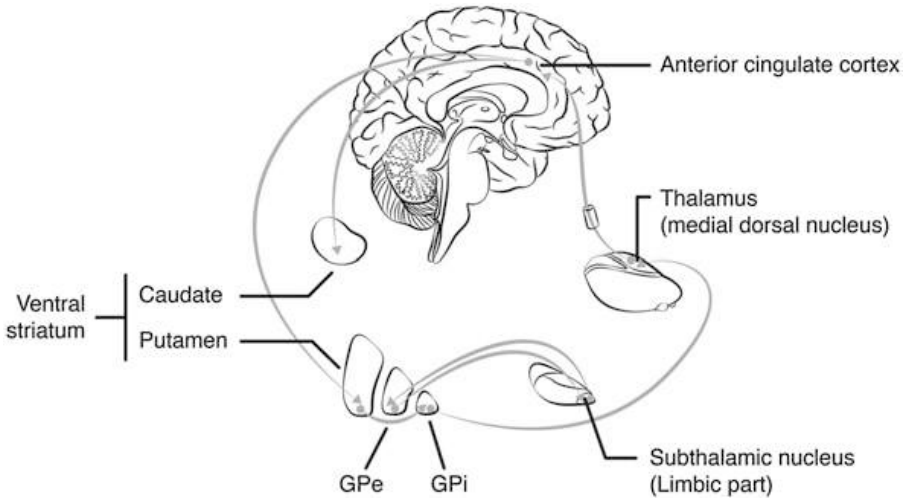

Fig. 2.28 The cortico-striato-thalamo-cortical (CSTC) limbic loop. According to [200]

limbic manifestations, and motor behavior. The same is true of the nucleus accumbens,[103] which is also an important interface between desire and action. The subthalamic nucleus (STN) may also, according to a French team led by B. Bioulac, serve a more complex function as the *central clock of the central basal ganglia* synchronizing the oscillatory activity of these nuclei with the activity in the cortex [210, 211]. These oscillations are essential to brain connectivity and plasticity [212].

The Neurotransmitter Circuits

Abstract Three main neurotransmitters, dopamine, serotonin, and norepinephrine, all monoamines, are involved in the neurochemical circuitry of the limbic system. Dopamine synthesized in the substantia nigra intervenes in CSTC loops while dopamine secreted by neurons in the ventral tegmental area is involved in the reward circuit. Serotonin synthesized in the raphe nuclei modulates behavior, primarily through inhibition, while noradrenaline synthesized in the locus coeruleus increases attention to external stimuli.

As we saw in the previous section, *dopamine* is at the heart of loop circuits. However, two other neurotransmitters must also be mentioned for their role in the limbic system: *serotonin*, which has an inhibitory effect on behavior, and *norepinephrine*, which has an excitatory effect on behavior. These neurotransmitters are primarily synthesized by neurons in the brainstem and released over wide areas of the brain creating a *diffuse regulatory system*.

[103] Cf. p. 129.

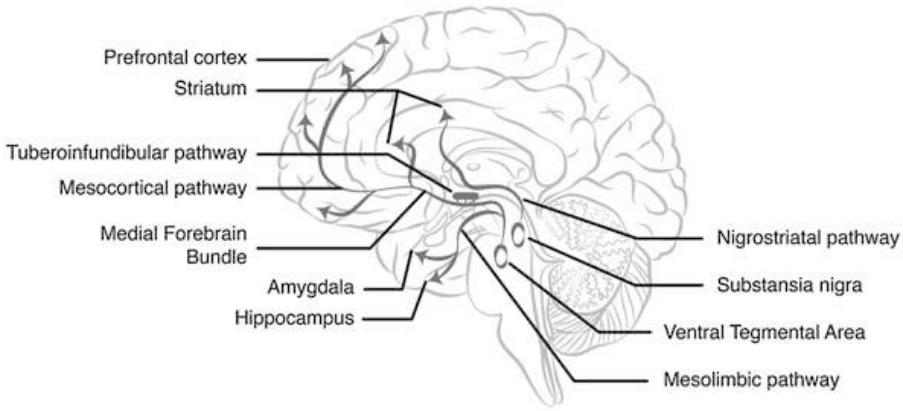

Fig. 2.29 The dopaminergic pathway

Dopamine and the Reward Circuit

Within the brain dopamine plays a critical role in motivity, cognition, motivation, sleep, and memory. Four major dopaminergic pathways can be identified according to where the molecule is being produced and released (Fig. 2.29).

Dopamine is synthesized mainly by neurons in the substantia nigra and the ventral tegmental area (VTA) whose axonal projections target the striatum or the septal nuclei. The dorsal part of the striatum receives dopaminergic projections from the SN along *the nigrostriatal pathway* and is involved in motor control.[104] The ventral striatum, however, receives dopaminergic afferents from the VTA along the medial forebrain bundle[105] (Fig. 2.30).

This second dopaminergic pathway, called *the mesolimbic pathway*, is of more particular interest to us because of its relation to the *limbic system*. The mesolimbic pathway is also called *the reward circuit* because of its involvement in the control of motivational and reward processes: it gives positive reinforcement to pleasurable behavior. In animals, lesions of the VTA result in neglect of the environment and reduced exploratory behavior. However, if electrodes are implanted in the VTA or along the MFB and the animal is allowed to freely auto-stimulate itself, it will engage in this highly gratifying behavior to the point of neglecting its basic

[104] Parkinson's disease is an example of a substantia nigra degenerative disease that provokes a rarefaction of dopamine. This deficiency in the cortico-striato-thalamo-cortical loop will generate a rarefaction of movement. In the other loops, associative and limbic (which are also dependent on this neuromediator), this dopamine insufficiency will manifest through cognitive problems (dementia) or psychiatric problems (depression, anxiety) also found in this neurologic disease.

[105] The medial forebrain bundle arises in the deep nuclei of the cerebellum and then becomes the periaqueducal gray matter. It then divides into two branches: an inferior and internal branch going to the lateral hypothalamus and a superior external branch projecting to the nucleus accumbens after transiting through the inferior part of the anterior limb of the internal capsule. This superior external branch projects to the orbifrontal, dorsolateral and probably the subgenual cortices [221].

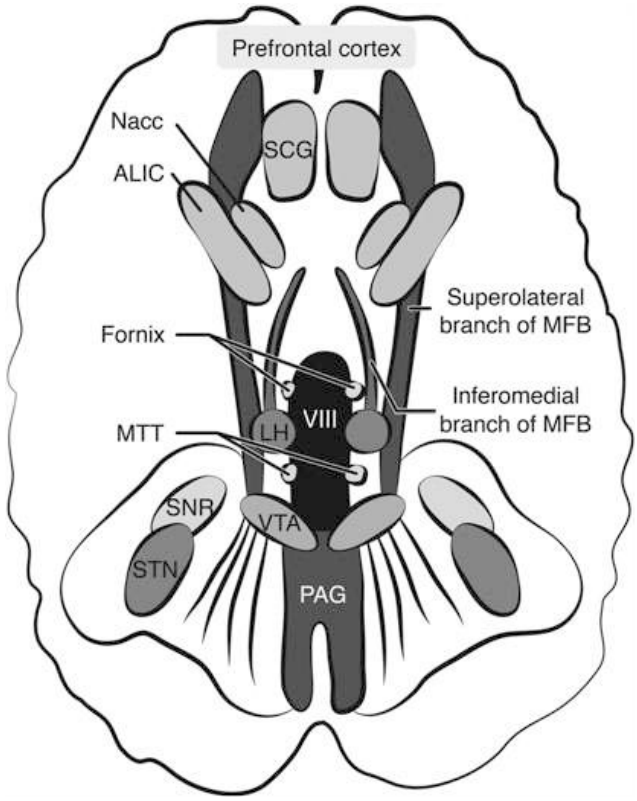

Fig. 2.30 Medial forebrain bundles *MFB*—top view of the brain. *VTA* Ventral Tegmental Area; *ALIC* Anterior Limb of the Internal Capsule, *MTC* Mammillothalamic Connections, *SGC* SubGenual Cortex, *NAcc* Nucleus Accumbens, *LH* Lateral Hypothalamus, *STN* SubThalamic Nucleus, *SNR* Substantia Nigra Reticulata, *PAG* Periaqueductal gray matter, 3 V: Third Ventricle. According to [222]

survival activities [90]. Reward and reinforcement phenomena are intended to help the subject delight in behaviors essential to survival such as eating and reproduction. In addition to these motivation and aversion processes, the mesolimbic system is also involved in certain cognitive functions. This circuit is co-opted when an individual takes drugs since all addictions, as discussed earlier have in common that they increase the concentration of dopamine in the nucleus accumbens. This dopamine production, which causes feelings of pleasure, leads to compulsive behavior in which drug-use replaces survival behaviors. The third dopamine pathway, *the mesocortical pathway*, is composed of dopaminergic neurons in the VTA whose axons project to the prefrontal cortex and in particular the anterior cingulate cortex. It is implicated in concentration and executive functions such as memory. The final bundle of dopaminergic neurons, the *tuberoinfundibular pathway*, arises in the hypothalamus and inhibits prolactin secretion in the anterior pituitary. Dopamine binds to two classes of receptors: D1 and D2 [213]. The D1-class is composed of post-synaptic receptors with excitatory effects. It includes the D1 receptors in the striatum, nucleus accumbens and cortex, and D5 receptors in the hippocampus and hypothalamus. The D2-class, pre- and post-synaptic, is inhibitory and includes the D2 receptors in the striatum, nucleus accumbens, d cortex and anterior pituitary, D3 in the ventromedial striatum and nucleus accumbens, and D4 in the cortex and the hippocampus. These last two receptors are less abundant in the brain. In schizophrenia, hyperactivity of the

mesolimbic pathway may, among other things,[106] be responsible for symptoms such as delusions and hallucinations. Conventional neuroleptics have the effect of blocking D2 receptors, thus reducing hallucinatory and delusional symptoms. However, these molecules have the disadvantage of binding to other pathways like the nigrostriatal pathway causing movement disorders (dyskinesia), or the mesocortical pathway, causing cognitive slowing, and the tuberoinfundibular pathway causing increased levels of prolactin.

Serotonin

All the neurons producing serotonin [5-hydroxytryptamine (5-HT)] within the brain are located in the medial part of the brainstem. They are the raphe nuclei (Fig. 2.31).

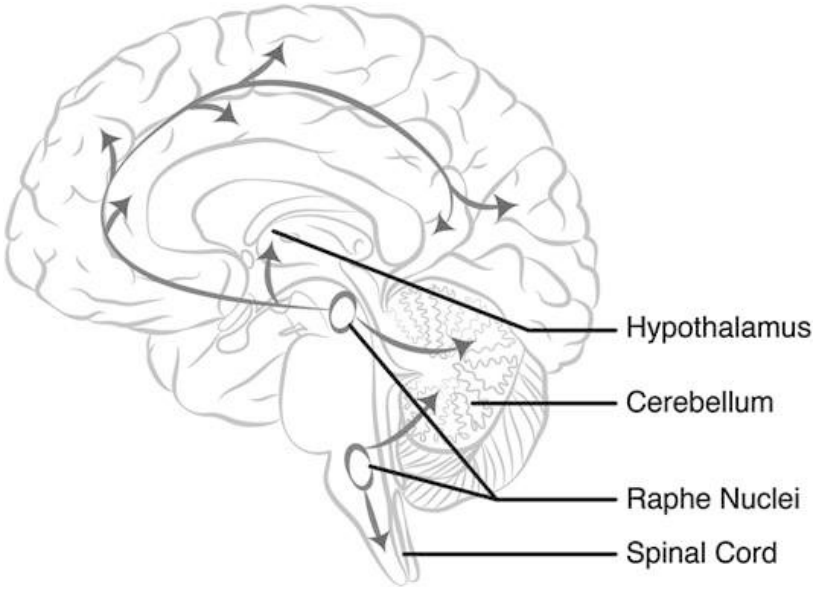

Fig. 2.31 The serotonergic pathway

[106] Multiple neurobiological hypothesis try to explain the symptoms of schizophrenia. Dopaminergic hypothesis, formulated in 1973, comes from the efficiency of chlorpromazine, which changed, as we saw, the way of dealing with this psychosis in the 1950s. The serotoninergic hypothesis is nowadays confronted by the fact that another drug—clozapine—efficient in treating delusional symptoms, possesses more affinity for certain serotonin receptors than for dopamine's. This is why it has the advantage of not provoking undesirable motor effects of first-generation neuroleptics. The glutamate, which plays a role in memorization, learning and brain development, like GABA, inhibitor neurotransmitter, were also involved. To this we can add neurodevelopmental hypothesis. Brain imaging developed the idea that schizophrenia could be a problem of cortical function. Events during pregnancy could disturb multiplication and neuronal migration as well. Genetic, as well as environmental factors, are also explored, given that 15 % of schizophrenias are congenital.

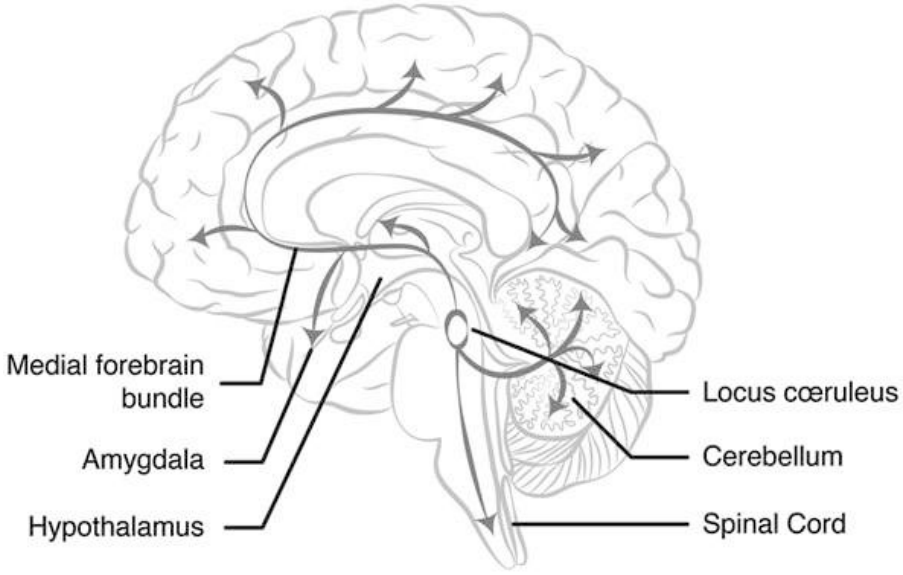

Fig. 2.32 The noradrenergic pathway

Their projections irrigate the entire central nervous system. In the lower part of the brainstem, these projections reach the spinal cord and modulate pain messages. Neurons in the upper part project throughout the brain and are involved in thermoregulation, regulation of mood, and the sleep–wake cycle.

Norepinephrine and the Stress Circuit

The nuclei secreting neurons are primarily located in a nucleus in the brainstem: thee locus cœruleus (Fig. 2.32).

This nucleus, which has close ties with the amygdala projects axons to almost all of the brain through a network of channels in common with dopaminergic neurons, within the MFB and serotonergic neurons. As with the amygdala, stimulation of the locus coeruleus causes anxiety behavior in animals, and conversely, the tranquilizing substances such as benzodiazepines, alcohol, or opiates decrease its activity. Norepinephrine is involved in operation of the body's alarm system via the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis (Fig. 2.15, p. 73). Norepinephrine is also involved alongside serotonin, in the regulation of attention and vigilance. Noradrenergic hyperactivity can lead to anxiety and hypoactivity to depression.

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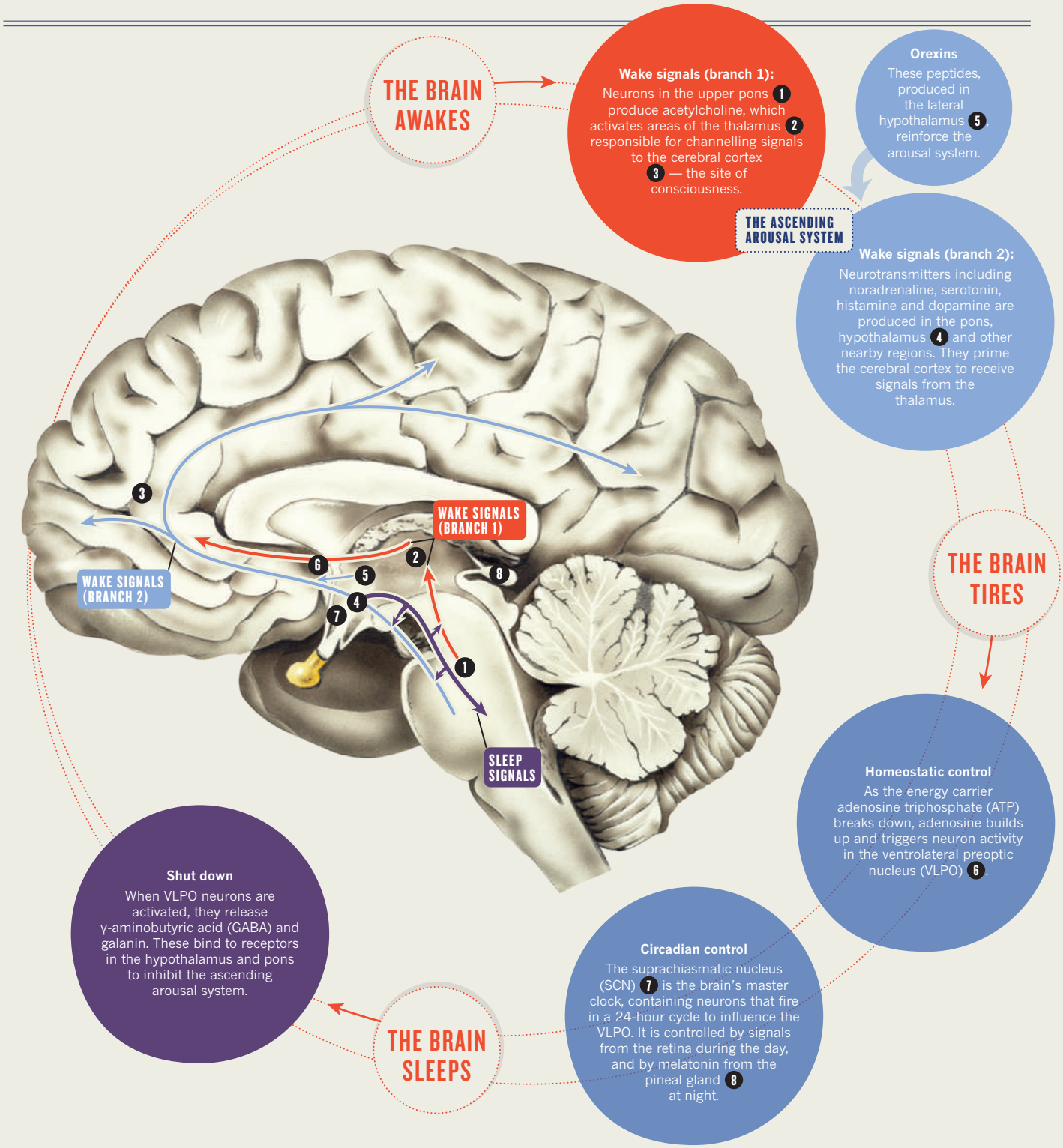
THE ANATOMY OF SLEEP

The ebb and flow of neurotransmitters switches our brains between sleep and wakefulness in carefully regulated cycles. By **Mark Peplow**.


THE BRAIN AWAKES
Wake signals (branch 1):
Neurons in the upper pons 1 produce acetylcholine, which activates areas of the thalamus 2 responsible for channelling signals to the cerebral cortex 3 — the site of consciousness.
Orexins
These peptides, produced in the lateral hypothalamus 5 reinforce the arousal system.
THE ASCENDING AROUSAL SYSTEM
Wake signals (branch 2):
Neurotransmitters including noradrenaline, serotonin, histamine and dopamine are produced in the pons, hypothalamus 4 and other nearby regions. They prime the cerebral cortex to receive signals from the thalamus.
WAKE SIGNALS (BRANCH 1)
WAKE SIGNALS (BRANCH 2)
SLEEP SIGNALS
THE BRAIN TIRES
Homeostatic control
As the energy carrier adenosine triphosphate (ATP) breaks down, adenosine builds up and triggers neuron activity in the ventrolateral preoptic nucleus (VLPO) 6.
Circadian control
The suprachiasmatic nucleus (SCN) 7 is the brain's master clock, containing neurons that fire in a 24-hour cycle to influence the VLPO. It is controlled by signals from the retina during the day, and by melatonin from the pineal gland 8 at night.
THE BRAIN SLEEPS
Shut down
When VLPO neurons are activated, they release γ-aminobutyric acid (GABA) and galanin. These bind to receptors in the hypothalamus and pons to inhibit the ascending arousal system.
KEY
1 UPPER PONS
2 THALAMUS
3 CEREBRAL CORTEX
4 HYPOTHALAMUS
5 LATERAL HYPOTHALAMUS
6 VENTROLATERAL PREOPTIC NUCLEUS (VLPO)
7 SUPRACHIASMATIC NUCLEUS (SCN)
8 PINEAL GLAND

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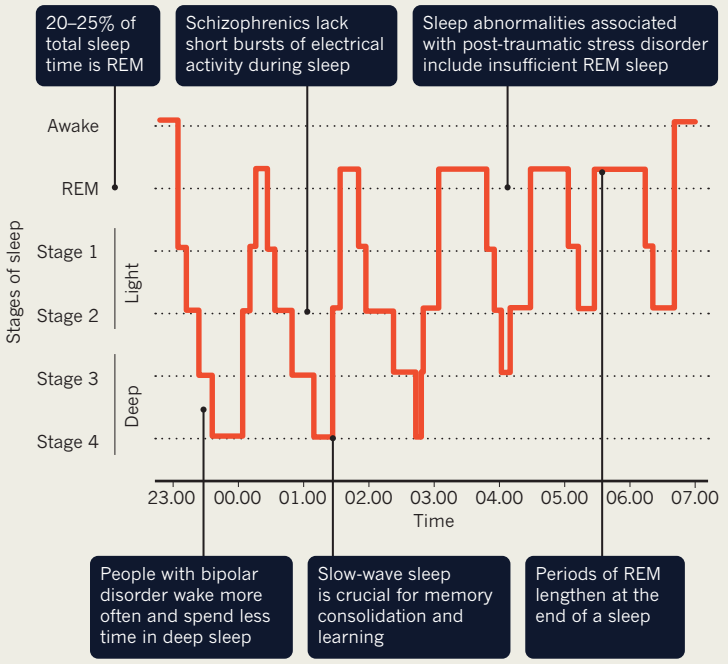
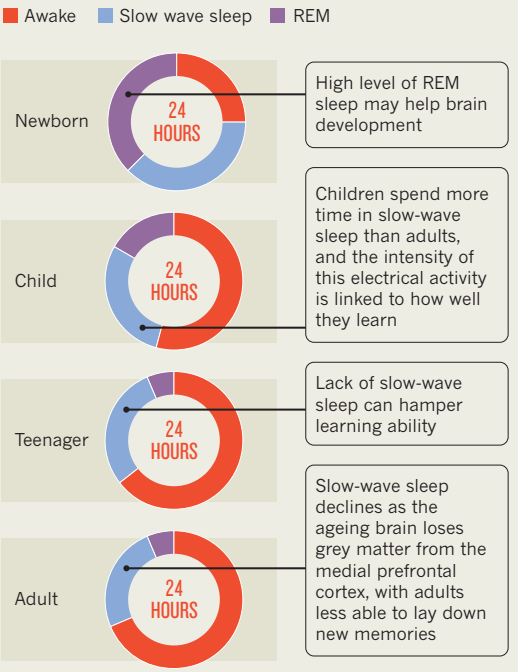
THE PHASES OF SLEEP

In a typical eight-hour sleep, the brain moves through different stages of electrical activity in repeating cycles that last about 90 minutes. Rapid eye movement (REM) sleep is linked to distinctive electrical activity in the brain, and is often associated with dreaming.



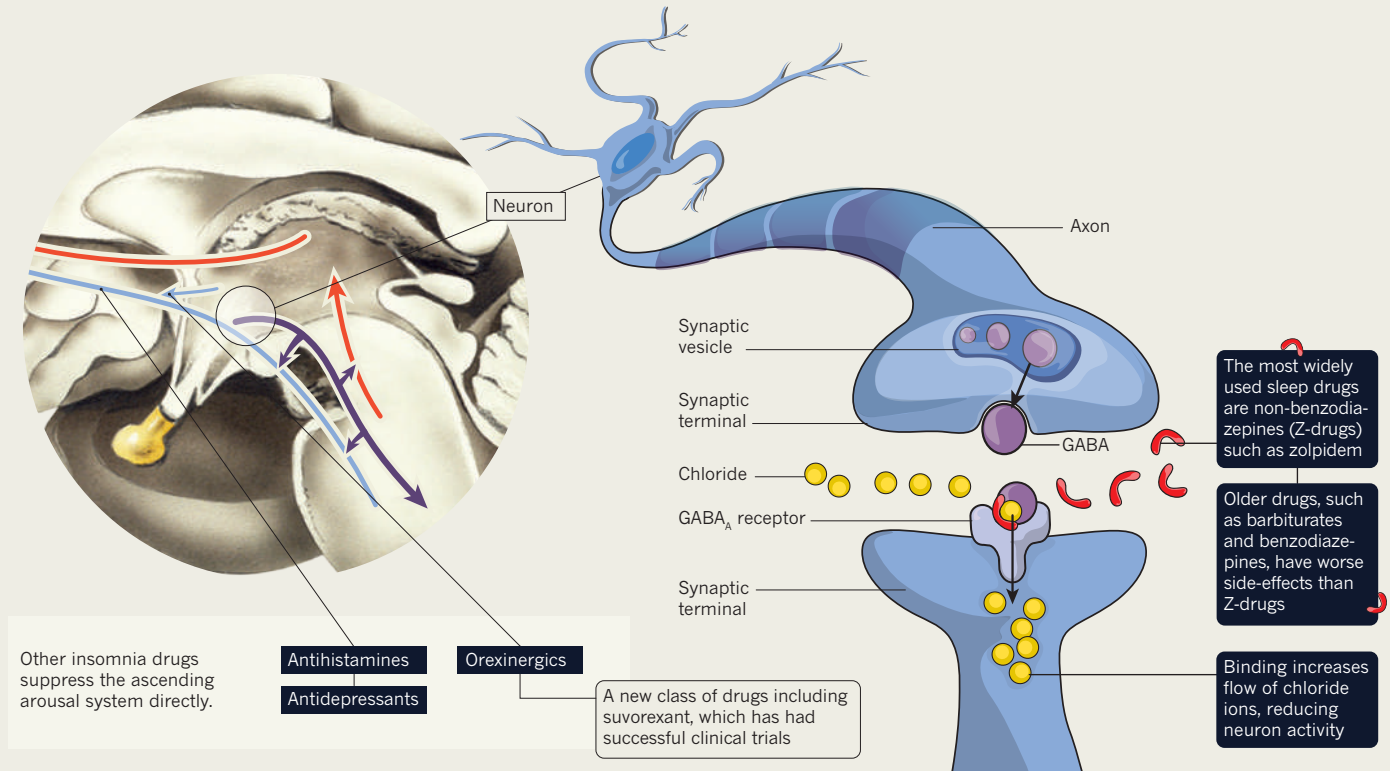
THE DECLINE OF SLEEP

After a childhood filled with blissful slumber, adulthood brings a decline in the quality and quantity of sleep.


Awake
Slow wave sleep
REM
Newborn
24 HOURS
High level of REM sleep may help brain development
Child
24 HOURS
Children spend more time in slow-wave sleep than adults, and the intensity of this electrical activity is linked to how well they learn
Teenager
24 HOURS
Lack of slow-wave sleep can hamper learning ability
Adult
24 HOURS
Slow-wave sleep declines as the ageing brain loses grey matter from the medial prefrontal cortex, with adults less able to lay down new memories

THE DRUGS OF SLEEP

The most widely used insomnia drugs promote sleep by improving the binding of γ-aminobutyric acid (GABA) to chloride ions released by the ventrolateral preoptic nucleus (VLPO) to suppress the ascending arousal system.


Neuron
Axon
Synaptic vesicle
Synaptic terminal
GABA
Chloride
GABA$_A$ receptor
Synaptic terminal
The most widely used sleep drugs are non-benzodiazepines (Z-drugs) such as zolpidem
Older drugs, such as barbiturates and benzodiazepines, have worse side-effects than Z-drugs
Binding increases flow of chloride ions, reducing neuron activity
Other insomnia drugs suppress the ascending arousal system directly.
Antihistamines
Antidepressants
Orexinergics
A new class of drugs including suvorexant, which has had successful clinical trials

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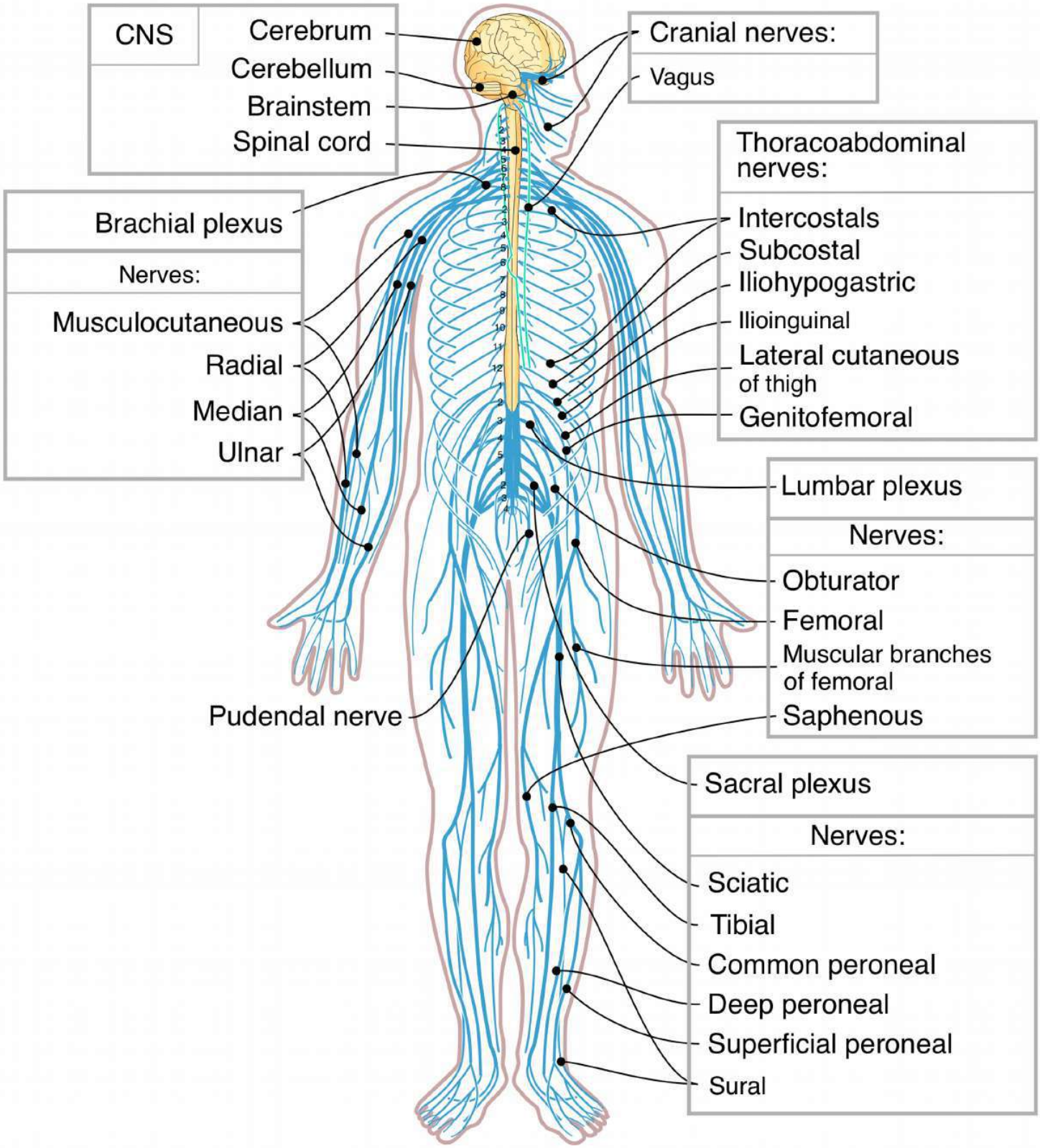
CNS
Cerebrum
Cerebellum
Brainstem
Spinal cord
Cranial nerves:
Vagus
Thoracoabdominal nerves:
Intercostals
Subcostal
Iliohypogastric
Ilioinguinal
Lateral cutaneous of thigh
Genitofemoral
Brachial plexus
Nerves:
Musculocutaneous
Radial
Median
Ulnar
Lumbar plexus
Nerves:
Obturator
Femoral
Muscular branches of femoral
Saphenous
Pudendal nerve
Sacral plexus
Nerves:
Sciatic
Tibial
Common peroneal
Deep peroneal
Superficial peroneal
Sural